TRANSACTIONS

OF THE

AMERICAN ASSOCIATION OF GENITO-URINARY SURGEONS

VOLUME XXXI

TRANSACTIONS

OF THE

AMERICAN ASSOCIATION OF GENITO-URINARY SURGEONS

Fiftieth Annual Meeting held at
Absecon, New Jersey

May 2, 3, and 4, 1938

Volume XXXI

UNIVERSITY OF MINNESOTA LIBRARY

Published for the Association by
The Bruce Publishing Company
Saint Paul and Minneapolis
1938

OFFICERS OF THE ASSOCIATION FOR 1937-1938

President

ALEXANDER RANDALL, M.D., Philadelphia

Vice-President

GEORGE GILBERT SMITH, M.D., Boston

Secretary-Treasurer

CHARLES C. HIGGINS, M.D., Cleveland
2020 East 93rd Street

Members of the Council

FRANK HINMAN, M.D., San Francisco
JOHN H. NEFF, M.D., University, Va.
THE PRESIDENT
THE VICE-PRESIDENT
THE SECRETARY
} *Ex-Officio*

1168385

JUL 7 '37 U OF M BINDERY (B-M)

LIST OF MEMBERS

HONORARY MEMBERS

DR. GARDNER W. ALLEN (1893), 146 Massachusetts Ave., Boston.
DR. GEORGE E. BREWER (1890), 19 East 65th Street, New York.
DR. CHARLES L. GIBSON (1901), The Burke Foundation, White Plains, N. Y.
DR. PAUL THORNDIKE (1892), 24 Marlborough Street, Boston.
DR. FRANCIS S. WATSON (1888), South Dartmouth, Mass.
DR. WILLIAM N. WISHARD (1889), 1711 N. Capitol Ave., Indianapolis.
(6)

CORRESPONDING MEMBERS

MR. E. HURRY FENWICK, C.B.E., F.R.C.S. (1906), 53 Bedford Gardens, Campden Hill, London, W. 8.
PROF. EMILE JEANBRAU (1911), 1 Rue Barthez, Montpelier, France.
MR. J. SWIFT JOLY, M.D., F.R.C.S. (1934), 80 Harley Street, London, W. 1.
PROF. FELIX LEGUEU (1929), 4 Rue Henri-Moissan, Paris VII, France.
PROF. DR. MED. A. VON LICHTENBERG (1929), Sanatorium Siesta, Budapest, Hungary.
MR. JOHN PARDOE, M.B., C.M., F.R.C.S. (1909), 1 Red House, Port Erroll, Aberdeen, Scotland.
PROF. ALFRED POUSSON (1909), 10 Cours Tournon, Bordeaux, France.
PROF. JEAN RENÉ VERHOEGEN (1911), 98 Rue Marie Thérèse, Brussels, Belgium.
*SIR JOHN W. THOMSON-WALKER, O.B.E., M.A., M.B., Ch.B., F.R.C.S. (1921), 96 Harley Street, London, W. 1.
PROF. DR. MED. HANS WILDBOLZ (1929), 12 Finkenhubelweg, Berne, Switzerland.
(9)

FELLOWS

DR. ROBERT C. BRYAN (1915), 1108 West Franklin Street, Richmond, Va.
DR. C. E. BURFORD (1926), 958 Arcade Building, St. Louis.
DR. HUGH CABOT (1907), Mayo Clinic, Rochester, Minn.
DR. CHARLES H. CHETWOOD (1900), 25 Park Avenue, New York.
DR. J. BAYARD CLARK (1906), 140 East 54th Street, New York.
DR. A. J. CROWELL (1921), Professional Building, Charlotte, N. C.
DR. JOHN H. CUNNINGHAM (1906), 46 Gloucester Street, Boston.
DR. F. C. EDGERTON (1906), 570 Park Avenue, New York.
DR. H. A. FOWLER (1907), 208 Stoneleigh Court, Washington, D. C.
DR. FRANCIS R. HAGNER (1906), 209 Columbia Medical Building, Washington, D. C.
DR. EDWARD L. KEYES (1901), 121 East 60th Street, New York.
DR. BRANSFORD LEWIS (1892), 609 Humboldt Building, St. Louis.

*Deceased.

Dr. William E. Lower (1912), 2050 East 93rd Street, Cleveland.
Dr. J. F. McCarthy (1924), 2 East 54th Street, New York.
Dr. David W. MacKenzie (1920), 305 Medical Arts Building, Montreal.
Dr. Henry H. Morton (1900), 32 Schermerhorn Street, Brooklyn.
Dr. Richard F. O'Neil (1909), 379 Beacon Street, Boston.
Dr. Alfred T. Osgood (1906), 65 E. 66th Street, New York.
Dr. James Pedersen (1906), 30 East 40th Street, New York.
Dr. Nathaniel P. Rathbun (1921), 80 Hanson Place, Brooklyn, N. Y.
*Dr. Henry L. Sanford (1916), 1622 Keith Building, Cleveland.
Dr. Louis E. Schmidt (1903), The Mallers Building, Chicago.
Dr. J. Bentley Squier (1906), 8 East 68th Street, New York.
Dr. Alexander R. Stevens (1916), 65 East 66th Street, New York.
Dr. Alfred C. Wood (1900), 2035 Walnut Street, Philadelphia.
Dr. Hugh H. Young (1901), Johns Hopkins Hospital, Baltimore.
(25)

ACTIVE MEMBERS

Dr. Nathaniel G. Alcock (1922), 201 Dey Building, Iowa City, Ia.
Dr. J. Dellinger Barney (1912), 87 Marlborough Street, Boston.
Dr. Benjamin S. Barringer (1911), 114 East East 54th Street, New York.
Dr. Montague Boyd (1921), 563 Capitol Avenue, S. W., Atlanta.
Dr. William F. Braasch (1913), Mayo Clinic, Rochester, Minn.
Dr. Henry G. Bugbee (1916), 2 East 54th Street, New York.
Dr. Hermon C. Bumpus (1923), 112 North Madison Ave., Pasadena, Calif.
Dr. J. E. Burns (1922), 1210 Professional Building, Kansas City, Mo.
Dr. George F. Cahill (1935), 121 E. 60th Street, New York.
Dr. John R. Caulk (1912), 723 University Club Building, St. Louis.
Dr. Arthur B. Cecil (1921), 1016 Pacific Mutual Building, Los Angeles.
Dr. Fletcher H. Colby (1931), 262 Beacon Street, Boston.
Dr. J. A. C. Colston (1921), Johns Hopkins Hospital, Baltimore.
Dr. E. G. Crabtree (1924), 99 Commonwealth Avenue, Boston.
Dr. John L. Crenshaw (1924), Mayo Clinic, Rochester, Minn.
Dr. Arthur H. Crosbie (1916), 520 Commonwealth Avenue, Boston.
Dr. Harry Culver (1924), 7 West Madison Street, Chicago.
Dr. Edwin Davis (1922), 1436 Medical Arts Building, Omaha.
Dr. Theo. M. Davis (1934), Finlay Bldg., Greenville, S. C.
Dr. Archie L. Dean, Jr. (1935), 30 E. 40th Street, New York.
Dr. Clyde L. Deming (1928), New Haven Hospital, New Haven, Conn.
Dr. G. S. Foulds (1934), 170 St. George Street, Toronto, Canada.
Dr. H. G. Fuller (1920), 209 Columbia Medical Bldg., Washington, D. C.
Dr. Joseph F. Geisinger (1933), Stuart Circle Hospital, Richmond, Va.
Dr. Roger C. Graves (1924), 12 Bay State Road, Boston.
Dr. B. H. Hager (1930), 1136 West 6th Street, Los Angeles.
Dr. Homer G. Hamer (1923), 1711 N. Capitol Avenue, Indianapolis.
Dr. Alex B. Hepler (1936), 752 Stimson Building, Seattle.

*Deceased.

Dr. Leon Herman (1933), 801 Medical Arts Building, Philadelphia.
Dr. Charles C. Higgins (1933), 2050 East 93rd Street, Cleveland.
Dr. Frank Hinman (1920), 384 Post Street, San Francisco.
Dr. T. Leon Howard (1936), 1224 Republic Building, Denver.
Dr. C. P. Howze (1934), 1801 Eye Street N. W., Washington, D. C.
Dr. Howard Jeck (1928), 745 Fifth Avenue, New York.
Dr. Herman L. Kretschmer (1916), 122 South Michigan Blvd., Chicago.
Dr. Thomas F. Laurie (1922), Medical Arts Building, Syracuse.
Dr. George R. Livermore (1922), 815 Medical Arts Building, Memphis.
Dr. E. J. McCague (1934), Mercy Hospital, Pittsburgh.
Dr. J. C. McClelland (1934), 170 St. George Street, Toronto, Canada.
Dr. Charles M. McKenna (1926), 25 East Washington Street, Chicago.
Dr. Gordon F. McKim (1935), Union Central Bldg., Cincinnati.
Dr. Henry O. Mertz (1930), 1711 N. Capitol Avenue, Indianapolis.
Dr. J. H. Neff (1929), University of Virginia, University, Va.
Dr. Reed M. Nesbit (1936), University Hospital, Ann Arbor.
Dr. Vincent J. O'Conor (1926), 55 East Washington Street, Chicago.
Dr. Clarence R. O'Crowley (1935), 31 Lincoln Park, Newark, N. J.
Dr. A. H. Paine (1922), 810 Medical Arts Building, Rochester, N. Y.
Dr. Frank S. Patch (1923), 1225 Bishop Street, Montreal, Canada.
Dr. Robin Pearse (1934), 170 St. George Street, Toronto, Canada.
Dr. William C. Quinby (1916), Peter Bent Brigham Hospital, Boston.
Dr. Alexander Randall (1920), 1323 Medical Arts Building, Philadelphia.
Dr. A. J. Scholl (1926), 1930 Wilshire Blvd., Los Angeles.
Dr. Thomas P. Shupe (1921), 1600 Keith Bldg., Cleveland.
Dr. Ira Sisk (1929), University of Wisconsin, Madison.
Dr. George G. Smith (1916), 6 Commonwealth Avenue, Boston.
Dr. William E. Stevens (1930), 490 Post Street, San Francisco.
Dr. Gilbert J. Thomas (1923), 1009 Nicollet Avenue, Minneapolis.
Dr. Miley B. Wesson (1932), 490 Post Street, San Francisco.

CONTENTS

FIRST DAY

May 2, 1938

1. Large and Multiple Renal Calculi in Children. CHARLES P. HOWZE... 1
2. Large Solitary Abscess of the Kidney. HOWARD S. JECK..... 21
3. Retroperitoneal Tumor Displacing Left Kidney. GEORGE R. LIVERMORE.. 29
Discussion
4. Observations on the Anatomic Basis of Congenital Polycystic Kidneys. ROBERT F. NORRIS and LEON HERMAN..... 41
5. The Association of Polycystic Disease of the Kidneys with Congenital Aneurysms of the Cerebral Arteries. C. R. O'CROWLEY and HARRISON S. MARTLAND..... 59
Discussion
6. Adenocarcinoma of the Kidney With Metastasis to the Lung. J. DELLINGER BARNEY and EDWARD D. CHURCHILL..... 71
7. Two Malignant Neoplasms of Urinary Tract. E. J. MCCAGUE..... 81
8. The Relation of So-Called Adenoma of the Kidney to Carcinoma of the Kidney. HUGH CABOT and ANTHONY W. MIDDLETON..... 91
Discussion

SECOND DAY

May 3, 1398

9. Adrenal Cortical Syndromes and Adrenal Tumors. GEORGE F. CAHILL.. 111
10. Adrenal Pheochromocytoma: The Syndrome of Paroxysmal Hypertension. DAVID W. MACKENZIE and DONALD MCEACHERN..... 127
Discussion
11. Multiple Primary Cancers. HERMAN L. KRETSCHMER..... 161
12. Endothelioma of the Corpora Cavernosa. GORDON S. FOULDS..... 189
Discussion
13. Pathologic Aspects of Experimental Aniline Tumors in the Bladder of Female Dogs. W. C. HUEPER..... 201
Discussion
14. Endometriosis of the Urinary Bladder. J. C. MCCLELLAND..... 215
15. New Methods of Irradiating Bladder Tumors. ARCHIE L. DEAN..... 221
16. Super-Voltage Radiation in the Treatment of Bladder Tumors. FLETCHER H. COLBY..... 227
Discussion

17. Transplantation of Endocrine Tissue. WILLIAM E. LOWER and EUGENE CUTULY 249

18. Non-Surgical Closure of Vesicovaginal Fistula. VINCENT J. O'CONOR. 255
Discussion

THIRD DAY

May 4, 1938

19. Resection of Prolapsed Mucosa at the Vesical Neck for Retention of Urine in the Female. JOHN H. NEFF..... 263

20. Aberrant Ureters Ending Blindly. WILLIAM J. ENGEL..... 271

21. Torsion of the Appendix Testis. ALEXANDER RANDALL..... 283
Discussion

22. Hypertension in Destructive Infected Unilateral Lesions of the Kidney. E. GRANVILLE CRABTREE..... 299

23. Renal Fusion: Urographic Data and Their Clinical Significance. WILLIAM F. BRAASCH and HOWARD J. HAMMER..... 321
Discussion

24. Early Phases of Prostatic Hyperplasia. CLYDE L. DEMING and CHARLES NEUMANN 339

25. Rhabdomyosarcoma of the Prostate in a Boy Seven Years of Age. GEORGE GILBERT SMITH and E. ROSS MINTZ..... 351

26. Prostatic Carcinoma with Extensive Intraprostatic Calcification. BENJAMIN S. BARRINGER and H. Q. WOODARD..... 363

27. Histologic Studies of the Effect of Irradiation on Hypertrophy of the Prostate. ROBERT A. MOORE, EDWARD L. KEYES and ALLISTER M. MCLELLAN 371

28. Factors Tending to Minimize the Prostatectomy Hazard. EDWIN DAVIS. 383
Discussion

29. Urinary Stone: Some Present-Day Concepts. WILLIAM C. QUINBY... 397

REMARKS BY THE PRESIDENT..... 405

THE AMERICAN ASSOCIATION OF GENITO-URINARY SURGEONS

FIRST DAY, MAY 2, 1938

LARGE AND MULTIPLE RENAL CALCULI IN CHILDREN

REPORT OF FOUR CASES

CHARLES P. HOWZE, M.D.
Washington, D.C.

The interesting medical and surgical problems arising in the management of large and multiple renal calculi in children have seemed to me of sufficient interest to warrant a report of four cases. In this small group, each patient offered different and rather unusual problems. Conservative surgery was the method of choice in all cases, in three of which there was coexisting pathology of the second kidney.

A study of the literature reveals the occurrence of renal stones in children to be relatively infrequent in this country. The largest collected series has been that of Thomas and Tanner. Kretschmer has recently reported a critical analysis of twenty-one personal cases. Campbell found nine urinary calculi in a study of 580 cases of chronic pyuria and only thirty-five in 10,360 autopsies in children under fifteen years of age. The data in regard to the size and multiplicity of calculi are not mentioned in several of the larger groups. Many individual and small groups have been reported and no doubt a considerable number similar to the cases I present have not reached the literature (Table I).

Urinary calculi have been found in the newborn by Southworth and Brendel. A staghorn stone one inch in diameter is reported by White in an infant of four and one-half months. In the foreign countries there seems to be a much higher percentage of calculi in children than is seen in this country. In the large series of cases reported by Civiale, Gross and others, approximately one-third to one-half of the cases occurred in children, while Hager and Magath report only thirty-three cases under fifteen years of age in 2,195 cases of stone at the Mayo Clinic.

The importance of the composition of urinary calculi has been stressed in recent years by many authors and has formed the basis of a more rational therapeutic attack to prevent postoperative recurrences. In some cases dissolution of calculi has occurred. Crowell demonstrated the dissolution of cystin calculi by means of

Author	Date	Sex	Age	Location	Single / Multiple	Type, composi
Puijn	1804	M	5	Both kidneys	M	sizes a
Prael	1825	F	6 months	Both kidneys	M	seed phosp
Harley	1864	M	10 months	Not stated	M	arley
Weir	1864	M	3	Pelves both kidneys	M	arge phospa te
Seligsohn	1874	F	7	Not stated	M	irly xalate
Arnozan	1886	M	14	Not stated	M	mor rugos te
Partridge	1886	F	20 months	Pelvis left kidney	S	hazeln
Pollard	1891	M	10	Pelvis right kidney	S	ns
Coulon	1895	M	3	Both kidneys	M	ravel
Pitt (3 cases)	1895	Not given	15, 11, 21 months	Pelvis (side not stated) in 2	S	1 ial; u
Ducamp d'Orgas (40 cases)	1897	M (27) F (13)	15 days to 2 years	Right kidney, 5; left kidney, 5; bilateral, 29; unstated, 1	S (6) M (33)	o gra
Comby (48 cases)	1899	M (31) F (17)	1 month to 2 years	Right kidney, 7; left kidney, 10; bilateral, 30; unstated, 1	S (11) M (37)	to urati
Neilson	1902	F	10	Pelvis right kidney	S	mm.
Monsseaux (77 cases)	1904	M (51) F (26)	1 to 15 years	Not stated	M	oxali grav
Jaffrey	1905	F	7	Left kidney	M	thar
Mandhle	1906	M	3½	Pelvis and calices of right kidney	M	o pi lim
Nash (2 cases)	1906	M	8 and 4 years	Pelvis left kidney in both	M S	30-2 id
Deutsche	1907	M	13	Convex border left kidney	S	hazel e; u
Dun	1908	F	6	Right kidney	S	6 ric a
Aleksinski	1910	M	7	Both kidneys	M	s size
Joseph (40 cases)	1911	M (27) F (13)	3½ weeks to 18 months	Right (10) Left (5) Bilateral (25)	M	d to and escri
Rafin (39 cases)	1911	M (24) F (11)	1 to 15 years	Right (21) Left (8) Bilateral (6)	Not stated	2-8 4 ox ; 4 4 2 u
Ruelle	1911	M	8	Left kidney	S	nut
Simpson	1911	M	8	Pelves and calices of both kidneys	M	u

Single or Multiple	Type, and Composition	Coexisting Pathology	Radiologic Report	Type of Operation	Remarks
M	sizes and shapes			Lithotomy	Autopsy
M	seed; rough; phosphate	Hematuria			Observed at autopsy
M	barley corns; uric				Observed at autopsy
M	large staghorn; phospate, triple te	Marasmus			Observed at autopsy
M	fairly large; calxalate and uric				Spontaneous passage
M	more than 25 rugose, calcium te	Coxalgia			Calculi apparently a sequela of medication with calcium phosphate
S	hazelnut	Inflammatory diarrhea			Observed at autopsy
S	ns	Hematuria		Nephrolithotomy	Recovery
M	gravels; uric acid	Hematuria			Postscarlatinal renal lithiasis; spontaneous passage of gravel
S	1 flattened, al; uric acid	Pollakiuria; pyonephritis; hematuria			Observed at autopsy
S (6) M (33)	to gravel; mostly	Arthropsy			Observed at autopsy
S (11) M (37)	to millet seed; uratic	Arthropsy; gastroenteritis; bronchopneumonia			Observed at autopsy
S	mm., 12½ gr.	Hematuria	Renal calculus	Nephrolithotomy	Recovery
M	oxalic, or phos- gravel	Hematuria			
M	than pea	Otorrhea	Calculi in left kidney	Nephrolithotomy	Recovery
M	pinhead; oxa- lime	Bronchopneumonia			Discovered at autopsy
M S	30-25 gr.; flat, id	Pollakiuria; hematuria	Negative in 1 case; calculus in left kidney region in other	Nephrolithotomy (in both cases)	Recovery (in both)
S	hazelnut; mulber- e; uric acid	Adenoids	Renal calculus in left kidney	Nephrolithotomy	Recovery
S	6 gr.; pyrami- ric acid	Hematuria	Renal calculus in right kidney	Nephrolithotomy	Recovery
M	s sizes and shapes	Hematuria, pyuria	Bilateral renal calculi	Bilateral nephrolithotomy	Recovery
M	d to millet seed; and composition escribed	Gastrointestinal disorders; pneumonia			Observed at autopsy
Not stated	2-8 gr.; 5 uric oxalic acid or ; 4 calcium phos- 4 calcium car- 2 urate-phos- 2 urate-oxalate	Hematuria	Positive in 13 operated cases	Nephrotomy 10; Nephrectomy 3	Recovery of all operated cases
S	nut	Albuminuria	Calculus in left kidney	Nephrolithotomy	Recovery
M	42 and 38 uric acid	Hematuria; pollakiuria	Bilateral nephrolithiasis	Bilateral nephrolithotomy	Recovery

Author	Date	Sex	Age	Location	Sing…e, T… Mul… Comp…
Ebert	1912	M	6	Pelvic region left kidney	S… hazel…
Ollerenshaw (2 cases)	1913	F	3	Pelvis left kidney	S… spi…
		M	8	Pelvis left kidney	S… r.; s… oxalat…
Reynard	1913	F	14	Pelvis right kidney	S… d; c…
Arquellada	1915	M	12	Right kidney	S… ated
Rodman	1915	M	12	Upper pole of right kidney and pelvis of left kidney	M… egg…
Farr	1916	F	6	Calices left kidney	M… ated
Lazelle	1916	M	7	Right kidney	M… mall,
Cifuentes (2 cases)	1917	M	7	Right kidney	M… ated
		M	6	Pelvis left kidney	S… be…
Gurgel	1917	F	6	Pelvis left kidney	M… eter… 0.01
Pool	1917	M	4	Pelvis left kidney	S… ston…
Portella	1917	F	4	Pelvis (side unstated)	M… ated
Moran	1919	F	5½	Both kidneys	M… ; ro…
Hill and Stevens	1920	F	3	Left kidney	M… ated
Jeanbrau	1920	M	10	Pelvis left kidney	S… nut
Mayet	1920	M	7	Both kidneys	M… ated
Thursfield	1920	F	10	Pelvis right kidney	S… f n…
Cassidy	1922	M	4	Pelvis left kidney	M… ated
Koenig	1922	M	11 months	Not stated	M… ated
Macalpine	1922	M	8	Calices of left kidney	M… rge… cys…
von Fekete	1923	M	6½ months	Pelvis left kidney	M… g…
Klein	1924	F	10	Right kidney	M… rge…
Beretervide and Pozzo	1924	M	9	Not stated	M… ze… ma… ate…

S OF ULUS IN CHILDREN—Continued

Sing[le] Mul[tiple], Type, and Composition	Coexisting Pathology	Radiologic Report	Type of Operation	Remarks
S[ingle] hazelnut; kidney	Pyelitis	Calculus pelvic region left kidney	Pyelolithotomy	Recovery
S[ingle] spiculate; uric	Hematuria	Calculus left kidney	Nephrolithotomy	Recovery
S[ingle] r.; spiculate; cal- oxalate and phos-	Pain and vomiting	Calculus lower pole left kidney	Pyelolithotomy	Recovery
S[ingle] d; calcium oxa-	Pyonephrosis	None	Nephrectomy	Recovery
S[ingle] ated		Calculus in right kidney	Nephrolithotomy	Recovery
M[ultiple] egg, almond, pea	Hematuria	One large stone in upper pole of right kidney; one large and two smaller in left kidney	Bilateral nephrolithotomy	Recovery
M[ultiple] ated	Pyonephrosis	Several calculi in calices lower portion left kidney	Nephrectomy	Recovery
M[ultiple] nall, round stones		Calculi in area right kidney	Nephrolithotomy	Recovery
M[ultiple] ated	Hematuria	Calculi in right kidney	Nephrolithotomy	Recovery
S[ingle] bean	Hematuria	Calculus in pelvis left kidney	Nephrolithotomy	Recovery
M[ultiple] ter larger of 0.014 mm.		Two calculi in pelvis of left kidney	Pyelolithotomy	Recovery
S[ingle] stone	Pyonephrosis right kidney	Calculus in left kidney	Pyelolithotomy (left) and later nephrectomy (right)	Recovery
M[ultiple] ated		Renal calculus	Pyelolithotomy	Recovery
M[ultiple] ; round; calcium	Anuria	Four large calculi in left, one large calculus in right kidney	Double nephrotomy	Recovery
M[ultiple] ated	Pyuria	Numerous calculi in left kidney	Nephrectomy	Recovery
S[ingle] nut	Hematuria	Calculus in pelvis left kidney	Pyelolithotomy	Recovery
M[ultiple] ated	Coxalgia; hematuria	Bilateral renal calculus		Operation advised but declined
S[ingle] f marble	Hematuria	Displaced kidney stone in pelvis	Nephrolithotomy	Recovery
M[ultiple] ated	Pyonephrosis; impacted urethral calculus	Multiple stones in pelvis left kidney	Nephrectomy	Recovery
M[ultiple] ated	Albuminuria; phosphaturia		Nephrotomy	Operation performed at age of 17 for chronic nephrolithiasis
M[ultiple] rge facetted, five cystin	Cystinuria	Calculi in calices left kidney	Nephrolithotomy	Recovery
M[ultiple] grape seed	Pyelitis, cystitis, pyelonephritis			Discovered at autopsy
M[ultiple] rge, 3 small	Nausea; vomiting	Calculi in pelvic region right kidney	Pyelolithotomy	Removal large stone; recovery
M[ultiple] ze of vetch; am- magnesio-calcium te	Calculous pyonephrosis; perinephritic abscess	Large renal calculi	Nephrectomy	Recovery

Author	Date	Sex	Age	Location	Single / Multi	Size, Co
Astraldi-Lanari	1925	M	4	Not stated	S	½ cn cretion
Haemmerle (2 cases)	1925	F	13	Lateral portions left kidney	M	n
		M	11	Pelvic region left kidney	M	mson sphate
LaFetra	1925	M	4	Pelves both kidneys	M	ge br
Lebenstein-Michel	1925	F	5	Near pelvis left kidney	M	ney s
Pulido Martin	1925	M	5	Calix of left kidney	S	state
Simons (2 cases)	1926	F	5	Pelvis right kidney	S	ge
		M	9	Pelvis left kidney	M	y sm
Deherripon	1927	M	3 months	Not stated	M	ight 3 rm; u calciu
Lignac (3 cases)	1929	M	9 months	Pelves both kidneys	M	ll; u
		M	7 months	Medullary papillæ both kidneys	M	ll; u
		M	5 months	Pelvis of right kidney	M	not
Belloni	1930	M	18 months	Pelvis left kidney	S	ge c
Lehucher and Jaubert de Beaujeu	1930	M	5	Parenchyma, calices, pelves both kidneys	M	nesiu
Behrens	1933	M	3½ months	Pelves both kidneys	M	til a e an ces
Schweizer, Llambias and Scatamacchia (2 cases)	1934	M	8	Pelvis left kidney	S	state
		M	5	Right kidney	M	state
Halbertsma (2 cases)	1935	M	20 months	Pelves and calices both kidneys	M	ll; c n p e cal
		M	5	Left kidney	S	ium race
Schonfeld	1935	F	14 months	Left and right renal region	M	larg
Sussi	1935	F	4	Pelves both kidneys	M	rry; erial
Bonnet	1936	M	15	Pelvis and calices of left kidney	M	oth, phate
Ermich	1936	M	9	Right ureter	S	nut; tion
Stoccada	1936	M	5	Pelves both kidneys	M	not phate

ingle or Multi	Size, Type, and Composition	Coexisting Pathology	Radiologic Report	Type of Operation	Remarks
S	½ cm.; phosphatic cretion	Asthenia; pyuria; hematuria	Calculus	Nephrotomy	Recovery
M	n	Pyonephrosis	Extensive incrustation	Nephrotomy	Recovery
M	mson seed; calcium sphate	Osteomyelitis	Calculous constellation suggesting dilated pyelon	Nephrotomy	Recovery
M	ge branching calculi		Extensive double renal lithiasis		Operation not permitted
M	ney shaped		Two calculi in pelvic region left kidney		Spontaneous passage
S	stated	Hematuria	Stone in one of calices of left kidney	Nephrotomy	Recovery
S	ge	Hematuria; pyelitis	Large stone in right renal pelvis		
M	y small	Hematuria	Multiple stones in left renal pelvis		
M	ght 3-9 ctg.; stalacrm; uric acid, traces calcium	Hematuria	Negative for calculi		Spontaneous passage
M	ll; uric acid-urate	Cloudy, swelling of kidneys			Observed at autopsy
M	ll; urate crystals				Observed at autopsy
M	not stated; uric				Observed at autopsy
S	ge chick-pea, uric	Acute glomerulo-nephritis			Specimen examined at autopsy
M	gnesium phosphate	Uremia; polyuria	Bilateral multiple calculosis		Death
M	til and smaller; le and earthy phosres	Renal colic	Numerous calculi in both kidneys, more on right than left		Recovery
S	stated	Vesical calculi	Renal lithiasis	Nephrolithotomy	Recovery
M	stated	Marked perinephritis	Calculi of right kidney	Lumbotomy	Death few hours after operation
M	ll; coral stone; calh phosphate and e calcium	Dysuria	Bilateral renal calculosis	Pyelotomy	Recovery
S	ium phosphate with race of oxalate	Dysuria	Calculus in left kidney		Spontaneous passage fragments of stone
M	large, two smaller	Perinephritic abscess; subarachnoid hemorhage	Large stone left, two small, in right renal region		Observed at autopsy
M	rry; soft fibrinous terial	Bilateral calculous pyonephrosis	Bilateral renal calculosis with pyonephrosis	Bilateral pyelotomy	Recovery
M	oth, round; calcium phate	Voluminous hydronephrosis	Enlarged pyelocalycine cavities	Nephrectomy	Recovery
S	nut; type and comtion not described	Dysuria	Right ureteral calculus	Ureterotomy	Recovery
M	not stated; calcium phate	Hematuria	Calculosis of renal pelves	Pyelotomy	Recovery

alkalinization therapy. Higgins has also obtained similar results with other types of stones by means of diet and vitamin A.

Case 2 of this series is of particular interest in that the dissolution of many small cystin calculi has taken place. The finding of a xanthine nucleus in Case 3 places it in the category of rare stones. Excellent articles on both cystin and xanthine calculi have been published by Kretschmer and on cystin by Ewell and others. It is not the purpose of this paper to discuss the present-day concepts of the etiology of these rarer types of calculi which have been thoroughly discussed by the authors mentioned above.

Case 1.—R. R., white, male, aged seven, was admitted to the Childrens Hospital January 29, 1933. The history was as follows: The child was apparently normal in every way until the age of three, when he had an attack of scarlet fever followed by a kidney complication, which was diagnosed nephritis by the family physician. Since this time, the child had repeated attacks of hematuria at irregular intervals. Urologic investigation was sought in September, 1932. The positive findings were anemia, pyuria grade 2, 40-60 R.B.C. to a microscopic field, many Gram-negative bacilli, and a mass in the left lumbar region, apparently an enlarged kidney. A plain radiograph of the urinary tract revealed an irregular staghorn shadow with an accessory round shadow in the right kidney region and a large renal shadow on the left (Fig. 1). An intravenous urogram three hours and forty minutes following the injection of skiodan disclosed a large left hydronephrosis and also a marked localized hydronephrosis of the upper pole of the right kidney (Fig. 2). We were thus confronted with the problem of a functionless left kidney and a right containing a large calculus with resultant destruction of the upper pole. Laboratory studies were as follows: Red blood cells 3,025,000; leukocytes 19,200; hemoglobin 55 per cent; non-protein nitrogen 38 mgm.; urea nitrogen 16 mgm.; urea 34 mgm.; "phthalein" excretion was 29 per cent in the first hour and 12 per cent in the second. Cystoscopy revealed a normal bladder. An obstruction at the left ureteropelvic junction was passed with difficulty and there followed a steady flow of pale cloudy urine which contained innumerable pus cells and Gram-negative bacilli on microscopic examination. The urine from the right kidney also contained many pus cells and bacilli. The function of the right kidney with indigo carmin was graded 3. No dye appeared through the left catheter in twenty minutes. The urea from the left kidney was 0.1 per cent. A poor prognosis was given but operation was insisted upon by the child's parents.

Operation was performed January 30, 1933. The right kidney was exposed through a lumbar incision. The upper pole was very thin and contained practically no renal parenchyma. An incision was made into the pelvis for the removal of the calculi. In removing the stag-

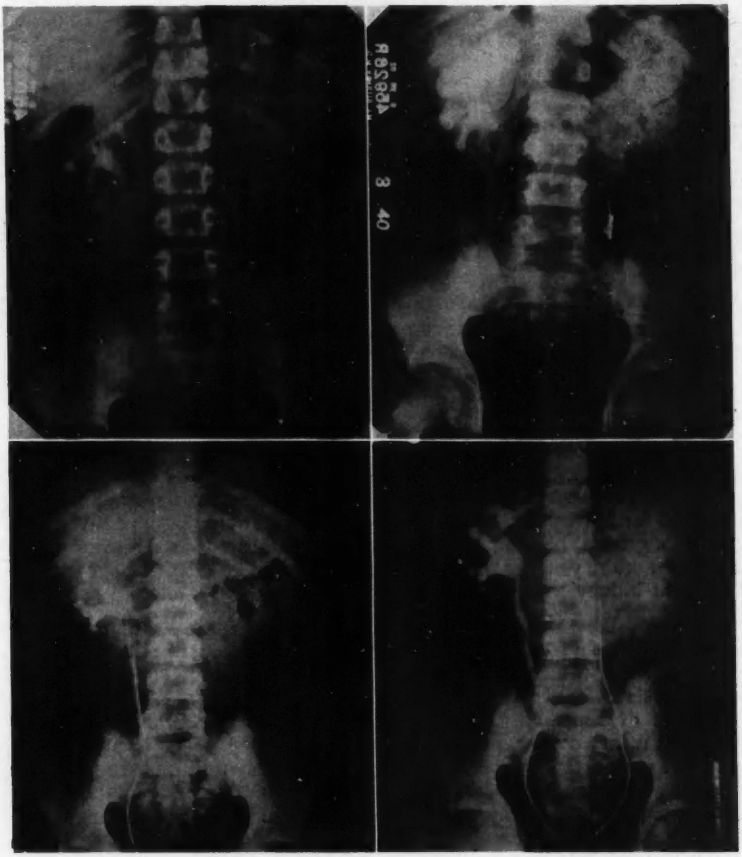


Fig. 1. Right staghorn calculus with accessory calculi in middle and lower calices. Large left renal shadow.

Fig. 2. Intravenous urogram; three hours, forty minutes. Localized hydronephrosis upper pole of right kidney. Large left hydronephrosis.

Fig. 3. Right pyelogram, three years following pelviolithotomy, renal resection and nephrotomy.

Fig. 4. Bilateral pyelogram, six years following operation.

horn calculus several calyceal spurs were broken. The fragments were removed by forceps and lavage. The upper pyonephrotic third of the kidney was resected. The pelvis was closed by interrupted sutures and the kidney with mattress hemostatic sutures. A tube was left in the pelvis for drainage. Convalescence was complicated by partial blockage of the left hydronephrosis which required indwelling catheter drainage for three days. The patient was discharged from the hospital four weeks following operation with the wound healed. No x-ray check was made at this time. The calculi were reported to be composed of calcium oxalate.

A subsequent study, two months following operation, disclosed two shadows in the right renal area. These were no doubt due to fragments left at operation. Repeated attempts at dissolution of the calculi through pelvic lavage with phosphoric acid, supplemented by urinary acidification and vitamin therapy, were of no avail.

At a second operation, January 23, 1934, the two calculi were removed through a small nephrotomy incision into the lower calix. Convalescence was again complicated by partial blockage of the left hydronephrosis, requiring indwelling catheter drainage. Since this time the patient has been seen at frequent intervals.

A right pyelogram (Fig. 3) three years after the second operation revealed a satisfactory pelvis. A recent study (April 19, 1938) again shows a good right pelvis. The left hydronephrosis remains unchanged and will doubtless require removal at a later date. The patient's general health is excellent despite the fact that the urine from the right kidney continues to show a low grade infection. Urea in the right kidney urine is 1.8 per cent and that of the left 0.3 per cent.

Case 2.—W. D., white, male, aged six, had been seen at Childrens Hospital on several occasions before urologic consultation was requested. His first admission was in November, 1935, at which time a diagnosis of tubercular mesenteric adenitis was made. The history was that of repeated attacks of left lower quadrant pain associated with vomiting, over a period of eighteen months. The urine at that time was reported to contain a moderate number of pus cells. The patient was again admitted to the hospital in April, 1936, with the same symptoms. X-ray examination revealed the heart, lungs and thymus normal. Abdominal radiographs disclosed no shadows suggestive of calcified mesenteric glands or calculi in either kidney region. The urine again contained a moderate number of pus cells. At the third admission, in May, 1937, the patient was referred for urologic study.

Physical examination resulted in essentially negative findings. The stain of the urinary sediment showed many Gram-negative bacilli and staphylococci. Repeated stains for tubercle bacilli were negative. Blood examination revealed the following: Wassermann negative; red blood cells 3,720,000; leukocytes 29,000; hemoglobin 56 per cent;

Fig. 5. Bilateral multiple calculi in a horseshoe kidney.

Fig. 6. Cystogram. Large bladder. No ureteral regurgitation.

Fig. 7. Two hour intravenous urogram. Faint upper left dilated caliceal shadows.

Fig. 8. Right ureterogram. Dilated tortuous ureter. Large calculus prevents dye from reaching the pelvis.

non-protein nitrogen 42 mgm.; calcium and inorganic phosphorus within normal limits. A tuberculin reaction was strongly positive. Plain radiograph of the urinary tract disclosed two large shadows surrounded by multiple small shadows in both kidney regions. There was a rather wide spinal defect between the fifth lumbar vertebra and the sacrum (Fig 5). The bladder was large as shown by the cystogram. There was no ureteral regurgitation (Fig. 6). There was

Fig. 9. Right and left ureterogram.
No opaque media in either pelvis.

only a faint shadow of opaque medium in the dilated upper calices of the left kidney two hours following the injection of diodrast (Fig. 7). Cystoscopy revealed a normal bladder. A right ureterogram showed a dilated tortuous ureter (Fig. 8). The left ureter was approximately normal in caliber and deviated sharply to the left as it entered the pelvis (Fig. 9).

The picture suggested that of a horseshoe kidney containing bilateral multiple stones. The prognosis seemed very poor indeed and the child was allowed to return home. He re-entered the hospital one month later with measles. During convalescence uremic symptoms developed, accompanied by severe pain in the left kidney region. The child's parents insisted on operative intervention.

The kidney was exposed through a left lumbar incision and the diagnosis of horseshoe kidney was confirmed. The two kidneys were joined at the lower pole by an isthmus of renal tissue. The pelvis was found anterior to the renal vessels. The pelvis was incised and one large and thirty smaller calculi were removed. A large nephrostomy tube was placed through the lower calix for drainage (Fig. 10).

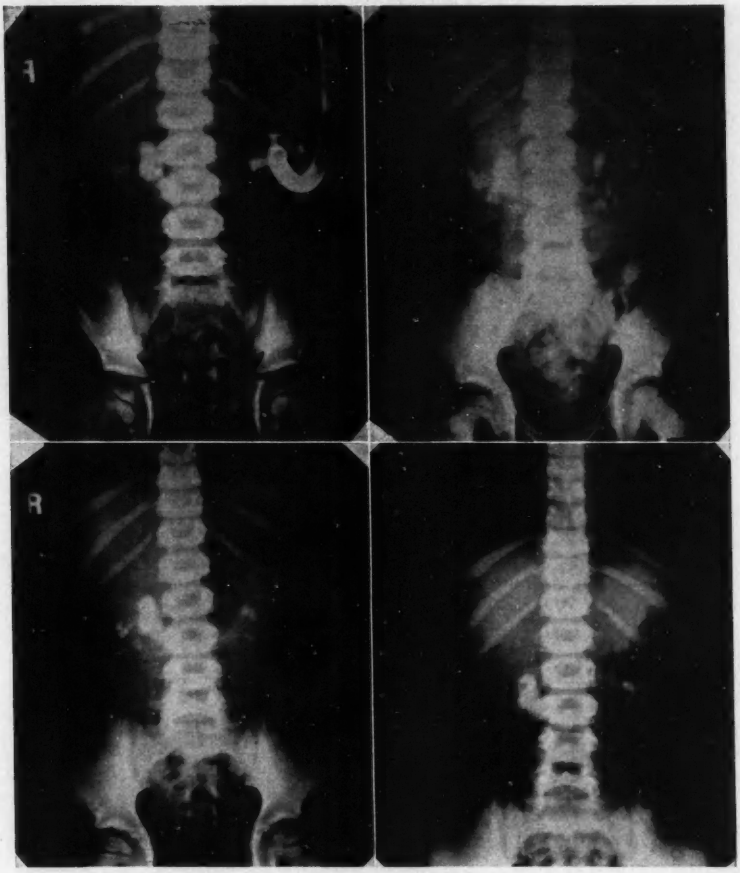


Fig. 10. Nephrostomy tube in left pelvis following removal of the large and thirty smaller calculi.

Fig. 11. Radiograph following removal of nephrostomy tube.

Fig. 12. Diminution of calculi in both renal pelves.

Fig. 13. Further diminution of calculi in both renal pelves.

The patient's condition did not permit a prolonged search for all of the smaller calculi. The calculi were yellow in color and waxy in appearance and proved on analysis to be pure cystin.

The patient improved slowly following operation. Several small calculi were removed through the nephrostomy tube by means of irrigation. Drainage was maintained for ten weeks, during which period the pelvis was lavaged twice daily with a solution of sodium bicarbonate. The urine pH has been maintained between eight and nine by means of sodium bicarbonate by mouth. Alkalinization therapy has been supplemented by a low protein diet and vitamin A. Under this regime dissolution of many of the smaller calculi has been accomplished (Figs. 11, 12 and 13). There seems some hope of completely freeing the kidney of these cystin calculi.

Case 3.—M. F., white, female, aged twenty-six months, was admitted to the Childrens Hospital January 6, 1936, with the following history: Three days after birth the child became acutely ill with nausea, vomiting and high fever, 105°. A specimen of urine, two weeks after birth, disclosed innumerable pus cells. Since this time, she had repeated similar attacks at two to three week intervals. The longest intermission between attacks was three months. A urologic study was made in another city in June, 1935, at which time a large shadow was noted in the right kidney region. The urine from the right kidney revealed many pus cells and B. coli; that from the left contained pus 1 and staphylococci. Since this time the attacks have become less frequent and have diminished in severity.

Physical examination resulted in essentially negative findings. Catheterized urine contained many pus cells. Ten to twenty red blood cells and many Gram-negative bacilli to a microscopic field. Cystoscopic examination revealed a normal bladder. The urine from the left kidney was normal, as were the excretions of indigo carmin. X-ray examination revealed a stag-horn shadow in the right kidney region and a smaller round shadow in the lower pole (Fig. 14). A left pyelogram was normal (Fig. 15). Blood studies showed a mild anemia, non-protein nitrogen 37.5, calcium 12.1 and inorganic phosphorus 2.3.

Operation: January 16, 1936, the right kidney was exposed through a lumbar incision. The kidney appeared normal in size, lobulated and there was a normal thickness of renal parenchyma. The staghorn and single calculi were exposed and easily removed intact through an inverted V incision in the pelvis, with the two limbs extending into the upper and lower calices, after the technic of Prather. The incision into the renal tissue was closed with hemostatic sutures, leaving a small tube in the pelvis for drainage.

Convalescence was uneventful. The patient was discharged from the hospital three weeks following operation with the wound healed. X-ray examination of the urinary tract revealed no abnormalities.

The child has not been examined personally since that time. A

recent report from the parents states that she has had no further symptoms referable to the urinary tract. An analysis of the small stone was of interest. It was laminated in three layers; the nucleus was reported pure xanthine, the outer layers were composed of triple phosphates.

Case 4.—M. M., white, female, aged eleven months, was referred for urologic study June 10, 1935. The child was apparently normal

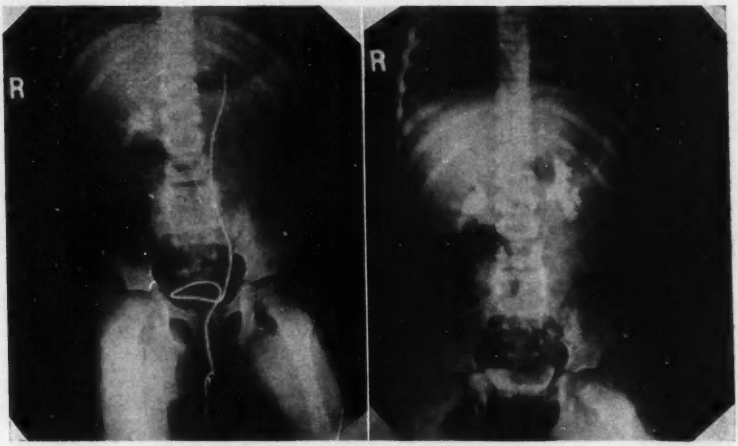


Fig. 14. Staghorn calculus with accessory stone in the right renal pelvis. Opaque catheter in left ureter.

Fig. 15. Staghorn calculus (right). Normal left retrograde pyelogram.

until the age of ten months, when she had an attack of fever with pyuria. Fever subsided, but pyuria continued. Physical examination was negative. Catheterized urine contained innumerable pus cells and many Gram-negative bacilli. Blood studies revealed a normal non-protein nitrogen and a mild anemia. Plain radiographs of the urinary tract revealed no shadows suggestive of calculi.

Cystoscopic examination disclosed a normal bladder mucosa. There were two ureteral orifices on the right. The left meatus was slightly smaller than normal. Urine from the lower pelvis of the right kidney was clear and microscopically negative; that from the left contained innumerable pus cells and bacilli. The excretion of indigo carmin from the right kidney was normal. There was some delay in its appearance from the left and the concentration was graded 2. A left pyelo-ureterogram revealed a dilated tortuous ureter with dilatation of the pelvis. The calices appeared small and cupped (Fig. 16).

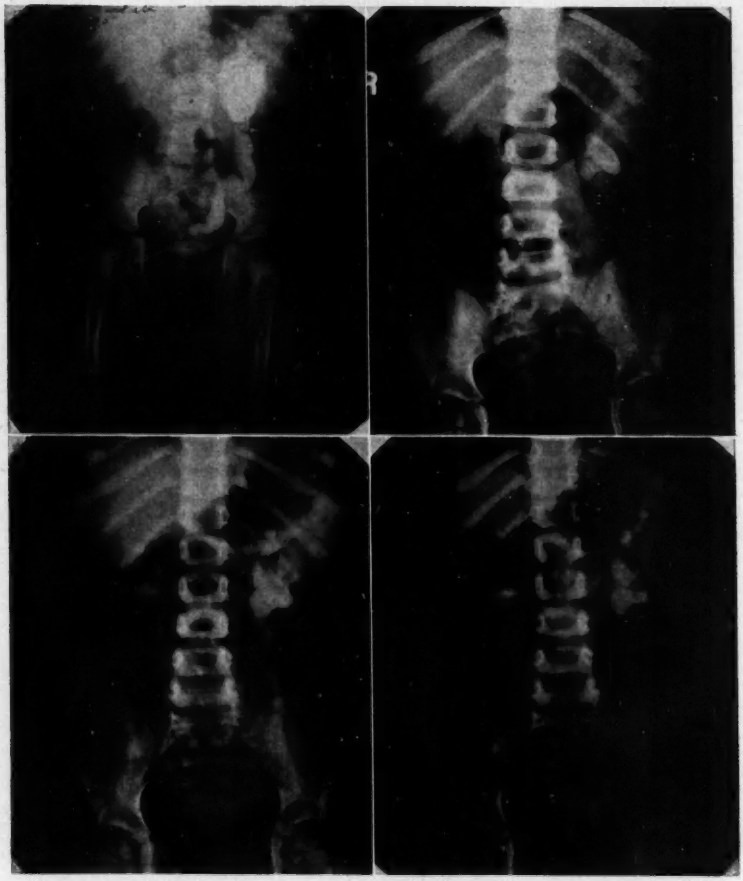


Fig. 16. Left retrograde pyelogram. Hydro-ureter and hydronephrosis.

Fig. 17. Multiple calculi in left kidney pelvis and lower left ureter.

Fig. 18. Intravenous urogram. Dilated pelvis and ureter (left). Reduplication of the ureter and pelvis (right).

Fig. 19. Intravenous urogram. Obstruction ureterovesical junction.

Four ureteral dilatations to No. 9F with pelvic lavage failed to improve the renal infection. The cause of the ureteral obstruction could not be definitely determined. A plain radiograph of the urinary tract in October, 1935, showed multiple faint shadows in the left kidney region. An increase in density of these shadows was noted in later radiographs. X-ray study, April 4, 1938, disclosed a number of calculi had passed into the lower ureter (Fig. 17).

Little change had occurred in the renal pelvis and ureter since the first pyelogram (Figs. 18 and 19). Due to the anomalous condition of the right kidney, predisposing to possible future disease, conservative surgery was advised with the hope of saving the remaining function of the diseased left upper tract.

Operation: On April 22, 1938, the left ureter was exposed at the pelvic brim through a low midline incision. The ureter was dilated to the size of the little finger and its walls thickened. The ureter was freed to its vesical entrance and no abnormal peri-ureteral bands or vessels, sufficient to account for any degree of obstruction, were found. The bladder was then opened. A grooved director was passed through the intramural ureter and the roof incised. Fourteen small calculi were then removed transvesically and the ureter intubated with a No. 16 F. soft rubber whistle tip catheter for kidney drainage. The bladder was drained with a No. 24 Pezzar catheter.

Convalescence to this date has been uneventful and a second operation to remove the renal calculi will be done in the near future. The ureteral stones were reported to be composed of calcium carbonate.

Second operation (May 9, 1938): The left kidney was exposed through a lumbar incision. The renal parenchyma appeared normal. The pelvis was slightly dilated. The ureter, which was thickened and tortuous, was freed to the pelvic brim. Six calculi were then removed through a pyelotomy incision. The indwelling ureteral catheter which had been placed at the first operation was allowed to remain for drainage and further splinting of the ureter.

The patient was discharged from the hospital on May 29, 1938, with both suprapublic and lumbar incisions healed. The urine became entirely free from pus cells and bacteria on July 19, 1938, and has remained normal for the past four months. Excretory urogram revealed marked improvement in the ureterectasis.

SUMMARY

1. Four cases of large and multiple renal calculi in children are reported.

2. Chronic pyuria is the predominating symptom in large calculi in children.

3. The occurrence of renal calculi with coexisting pathologic

lesion of the second kidney makes conservative surgery imperative in many cases.

4. The possibility of the dissolution of cystin calculi by medical means demands a more careful study of the urine for cystin crystals in all children showing urinary stones.

5. Urinary tract surgery is well tolerated by children and gratifying results can frequently be obtained in cases with badly damaged kidneys.

BIBLIOGRAPHY

ALEKSINSKI, I. P.: Bilateral nephrolithiasis in a child (Russian). Syezd Rossiysk. Khirurg., 9:191-194, 1910.

ARNOZAN, H.: Calcul phosphatique chez un enfant soumis à l'usage du phosphate de chaux. Jour. de méd. de Bordeaux, 16:74, 1886-87.

ARQUELLADA, A. M.: Un caso operado de cálculo de riñon en un niño de doce años. Pediatria españ., 4:50-52, 1915.

ASTRALDI and LANARI, E. L.: Sobre un caso de litiasis renal en un niño de 4 años. Semana méd., 32:pt.2, 805, 1925.

BEHRENS, W.: Nierensteinkolik im frühesten Kindesalter. Ztschr. f. Kinderheilk., 55:637, 1933.

BELLONI, G.: Osservazioni e reperti istologici del rene in un caso di calcolosi renale in un bambino di 18 mesi. Riv. di clin. pediat., 38:384-397, 1930.

BERETERVIDE, E., and POZZO, F.: Pionefrosis calculosa en un niño de 9 años. Rev. Asoc. méd. argent., 37:126-137, 1924.

BONNET: Un cas de calculs multiples du rein gauche chez un enfant de 15 ans. Arch. d. mal. d. reins, 10:189-193, 1936-37.

BRENDEL: Cited by Hunt, W., in: Keating, J. M. Cyclopedia of diseases of children. Philadelphia: Lippincott & Company, 3:596-632, 1890.

CAMPBELL, M. F.: Pediatric urology. New York: Macmillan Company, 1937.

CASSIDY, H. C.: Nephrolithiasis, pyonephrosis, and impacted urethral calculus in a boy of four. Canad. Med. Assn. Jour., 12:246, 1922.

CIFUENTES, P.: Dos casos de cálculos renales en niños. Pediatria españ., 6:82-87, 1917.

CIVIALE, J.: Traité de l'Affection Calculeuse. Paris: Crochard & Cie., 1838.

COMBY, J.: Lithiase rénale chez les enfants. Arch. de mèd. d. enf., 2:577-600, 1899.

COULON, G.: Lithiase rénale chez un enfant de trois ans, ayant fait sa première apparition à la suite d'une scarlatine. Méd. inf., 2:579-582, 1895.

CROWELL, A. J.: Cystin nephrolithiasis. Jour. Urol., 11:545-557, 1924.

DEHERRIPON: Lithiase rénale (coliques néphrétiques, hématurie, anurie de sept jours) chez un nourrisson de 3 mois. Bull. Soc. de pédiat. de Par., 25:460-463, 1927.

DEUTSCHE, W. S.: Nephro-lithotomy in a thirteen year old boy. Quart. Bull. Med. Dept. Wash. Univ., 5:100, 1906-07.

DUCAMP D'ORGAS, C.-P.-E.: La lithiase rénale dans la première enfance. Dissertation. Paris, 1897.

DUN, R. C.: A case of renal calculus in a child. Liverpool Med.-Chir. Jour., 29:154-157, 1908.

EBERT, O.: Nierensteine im Kindesalter. Med. Klin., 8:399-401, 1912.

ERMICH, S.: Renal lithiasis in children (Polish). Polska gaz. lek., 15:721-723, 1936.

EWELL, G. H.: Cystine nephrolithiasis. Jour. A.M.A., 99:2160-2166, 1932.

FARR, C. B.: Renal calculus, pyonephrosis, and perinephritic abscess in child of six. Phila. Gen. Hosp. Rep., 10:181-184, 1916.

GROSS, S. D.: System of Surgery. 4th edition. Philadelphia: Lea, 1866.
GURGEL, N.: Lithiase renal na infancia. Brazil-med., 31:327-365, 1917.
HAEMMERLE, O.: Ueber das Vorkommen von Nierensteinen im Kindesalter. Dissertation. Frankfurt a. M., 1925.
HAGER, B. H., and MAGATH, T. B.: Formation of vesical calculi. Jour. AM.A., 90:266-272, 1928.
HALBERTSMA, T.: Nepholithiasis in children (Dutch). Maandschr. v. kindergeneesk., 5:89-101, 1935.
HARLEY, G.: Three calculi removed from the kidney of a child aged ten months. Tr. Path. Soc. Lond., 15:150, 1864.
HIGGINS, C. C.: Urinary lithiasis; experimental production and solution with clinical application and end-results. Jour. Urol., 36:168-177, 1936.
HILL, M. C., and STEVENS, A. R.: Nephrolithiasis in a girl of three. Arch. Pediat., 37:615, 1920.
JAFFREY, F.: A case of multiple renal calculi in a girl of seven. Rep. Soc. Study Dis. Child., 6:74, 1905-06.
JEANBRAU, E.: Présentation d'un petit garçon de dix ans opéré d'un calcul du rein par pyélotomie. Montpel. méd., 41:297, 1919-20.
JOSEPH, H.: Ueber Nephrolithiasis im Säuglingsalter. Arch. f. path. Anat., 205:335-345, 1911.
KLEIN, S.: Nephrolithiasis in children, with report of a case. Arch. Pediat., 41:505-509, 1924.
KOENIG, F.: Zur Entstehung von Nierensteinen in den ersten Lebenswochen. Münch. med. Wchnschr., 69:1426-1427, 1922.
KRETSCHMER, H. L.: Stone in urinary tract in children; critical study of 21 cases. Am. Jour. Dis. Child., 52:513-527, 1936.
KRETSCHMER, H. L.: Xanthine calculi; report of case and review of literature. Jour. Urol., 38:183-193, 1937.
LA FETRA, L. E.: Large bilateral kidney stones in a child of five. Tr. Am. Pediat. Soc., 37:57-59, 1925.
LAZELLE, H. G.: Renal calculi in a child of seven; operation. Northwest Med., 15:403-405, 1916.
LEBENSTEIN, J., and MICHEL, L.: Case of renal calculus in a child of five. Med. Rev. of Rev., 31:74-76, 1925.
LEHUCHER, P., and JAUBERT DE BEAUJEU, A.: Polymicro-calculose rénale bilatérale chez un enfant de cinq ans. Gaz. med. de France (Rad. Suppl. No. 2), 33-35, 1930.
LIGNAC, G. O. E.: Over niersteenvorming bij kinderen in het eerste levensjaar. Nederl. tijdschr. v. geneesk., 75:pt.1, 3008-3013, 1929.
MACALPINE, J. B.: Specimen of cystin calculi from the kidney of a child. Proc. Roy. Soc. Med., Sect. Urol., 15:36, 1921-22.
MANDHLE, D. B.: A case of renal calculi in a child. Lancet, 1:1691, 1906.
MAYET, H.: Calculs dex deux reins chez un enfant immobilisé pour mal de Pott. Paris chirurg., 12:132-139, 1920.
MONSSEAUX, A.: Sur la lithiase rénale chez les enfants. Rev. mens. d. mal. de l'enf., 22:205-228, 1904.
MORAN, P.: Calculs des deux reins chez une enfant de cinq ans et demi. J. d'urol. méd. et chir., 8:463-467, 1919.
NASH, W. G.: Two cases of renal calculus in children under ten. Rep. Soc. Study Dis. Child., 6:188-191, 1905-06.
NEILSON, T. R.: Renal calculus in a child of ten. Ann. Surg., 36:283, 1902.
OLLERENSHAW, R.: Report of two successful cases of nephrolithotomy in young children. Brit. Med. Jour., 1:112, 1913.
PARTRIDGE: Specimen of renal calculus removed from an infant. Am. Jour. Obst., 19:153, 1886.
PITT, G. N.: Renal calculus in infants. Tr. Path. Soc. Lond., 46:90, 1894-95.
POLLARD, B.: A case of nephrolithotomy in a boy aged ten. Tr. Clin. Soc. Lond., 24:174-177, 1891.

Pool, E. H.: Nephrolithiasis and pyonephrosis in a child. Ann. Surg., 65:258-260, 1917.
Portella, P.: Calculose renal; nephrectomias na infancia. Brazil-med., 31: 318, 1917.
Prael, F.: Nierensteine bei einem sechsmonatlichen Kinde. Arch. f. med. Erfahr., 2:250, 1825.
Puijn, J.: De nieren door steenen opgevuld, in een jongen van vyf jaren. Natuurk. Verhandel. v. de Bataafsche Maatsch. d. Wetensch. te Haarlem, 2: pt. 2, 265-268, 1804.
Pulido Martin, A.: Un cálculo renal en un niño de cinco años. Siglo méd., 75:469-471, 1925.
Rafin: De la lithiase rénale et urétérale chez l'enfant. Ann. d. mal. d. org. génito-urin., 1:481-513, 1911.
Reynard: Pyonephrose calculeuse chez une fillette de quatorze ans. Lyon méd., 120:1305, 1913.
Rodman, J. S.: Nephrolithiasis in childhood. Tr. Phila. Acad. Surg., 17:233-237, 1915.
Ruelle, H.: Calcul du rein chez un enfant de huit ans. Centre méd. et pharm., 17:232, 1911-12.
Schonfeld, W. A.: Renal calculi in an infant, complicated by perinephritic abscess and subarachnoid hemorrhage. Am. Jour. Dis. Child., 1:686-692, 1935.
Schweizer, F., Llambias, A., and Scatamacchia, N.: Litiasis renal infantil. Actas Congr. nac. méd., 5:pt.4, 1069-1074, 1934.
Seligsohn: Ueber Nieren-Concremente im kindlichen Alter. Verhandl. d. Berl. med. Gesellsch., 5:2-5, 1874.
Simons, S.: Twee gevallen van nephrolithiasis bij kinderen. Nederl. tijdschr. v. geneesk., 70:pt.1, 1290-1292, 1926.
Simpson, G. C. E.: A successful case of bilateral nephrolithotomy for multiple calculi in a boy of eight. Liverpool Med.-Chir. Jour., 31:397-403, 1911.
Southworth: Quoted by Campbell (loc. cit.).
Stoccada, F.: Litiasi renale bilaterale contemporanea in bambino di anni cinque. Arch. ital di urol., 13:346-359, 1936.
Sussi, L.: Contributo allo studio dei calcoli molli fibrinosi batterici del rene dell' infanzia. Ann. ital. di chir., 14:301-316, 1935.
Thomas, G. J., and Tanner, C. O.: Urinary lithiasis in children. Jour. Urol., 8:171-183, 1922.
Thursfield, H.: Diagnosis of case of renal calculus in a child. Proc. Roy. Soc. Med., Sect. Dis. Child., 14:95, 1920.
von Fekete: Zum Tode führende Nierensteine bei einem 6½ Monate alten Säuglinge. Fortschr. d. Med., 41:93-95, 1923.
Weir, G.: Case of renal calculus in a child Edinb. Med. Jour., 10:69-71, 1864.
White, H. P. Winsbury: Stone in the urinary tract. Philadelphia: Blakiston's Son & Company, 1929.

LARGE SOLITARY ABSCESS OF THE KIDNEY

HOWARD S. JECK, M.D.

From the Urological Service of Bellevue Hospital, New York City

By solitary abscess of the kidney is meant an abscess which lies wholly within the kidney parenchyma and communicates neither with the kidney pelvis nor the perinephritic space. According to the literature of the past twenty years, large solitary abscess of the renal parenchyma is not often seen and less often recognized pre-operatively. However, there have been reported a comparatively large number of multiple cortical abscesses of the kidney, perinephric abscesses and kidney carbuncles†—similar lesions having in all probability etiological factors identical with those of the solitary abscess.

It was thought worth while to report the following two cases of solitary renal abscess not only because very few have apparently been recognized pre-operatively but also because the second case presents a rather interesting pyelographic demonstration of the seeming rapidity with which a diseased kidney may resolve following operation.

Case 1.—A man, twenty-two years of age, was admitted to the Bellevue Urological Service, on January 15, 1938, with the chief complaints of pain in the left side, chills and fever and loss of strength.

Three months before admission, the patient had had some type of infection of his left hand. Three weeks before admission the patient noted a discomfort in his left side.

On admission to the Bellevue Urological Service January 15, 1938, physical examination disclosed fairly marked tenderness in the left costo-vertebral region and slight tenderness anterior to the left kidney. Palpation in the right loin disclosed no abnormalities. The urine was grossly clear and was negative for albumin, sugar and pus cells. His temperature on admission was 100^{3} F. degrees and this gradually increased to 101^{2} degrees the day of his operation. Intravenous urograms made on the day of admission indicated an incomplete filling of the left kidney pelvis and fixation of the left kidney. In one of the radiographs the edge of the psoas muscle was fairly distinct

†Graves and Parkins, in their excellent article entitled "Carbuncle of the Kidney," brought the number of reported kidney carbuncles up to sixty-seven, including one of their own. They also cite fifteen additional cases which were reported between the writing of their article and its publication in the latter part of 1935, thus making the total number eighty-two at that time.

for a distance of about 8 cm. in its upper portion. The right urogram indicated a normal kidney on that side. Two days after admission a white blood count showed 15,800 cells with 83 per cent polymorphonuclear cells.

A tentative diagnosis of perinephritic abscess was made, and, because the patient appeared to be quite sick and his temperature was increasing, it was thought best to explore the left kidney region without further delay. This was done by means of the usual oblique kidney incision below and parallel to the last rib. The operator found the perirenal tissues (retrorenal fascia and perinephritic fat) to be thickened and pale. No free pus was found anywhere, however, in exposing the kidney proper, and it was not until the fatty capsule of the kidney had been completely removed that an area of fluctuation was detected about the mid-portion of the posterior curvature of the kidney (Fig. 1). This fluctuating area was opened and about 2 ounces of heavy pus were evacuated. Material was taken for a culture. Drains were inserted and the wound was closed in layers. The patient's temperature became normal the ninth postoperative day and remained so until his discharge from the hospital about one month after the operation. Before leaving the hospital both ureters were catheterized and, according to the urea and indigo-carmine tests, the functioning capacities of the two kidneys were about equal. Both ureteral specimens were grossly clear.

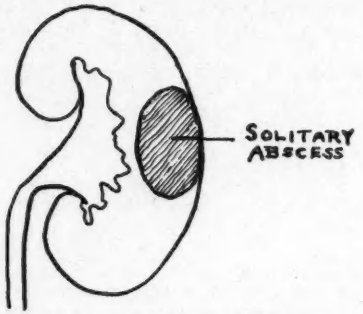


Fig. 1. Case 1. Approximate position and comparative size of abscess.

The patient made an uneventful recovery and three weeks after the operation both kidneys functioned well and about equally.

Case 2.—A young woman, twenty-seven years old, was admitted to one of the medical services of Bellevue Hospital on November 25, 1937, with the chief complaints of pain in the left side, chills and fever.

This patient stated that she had had chills and fever for one week

before entering the hospital. At one time her temperature went to 104, but on admission to the hospital it was only 101[2]. She also complained of pain in the left lower quadrant which alternated with similar but less marked pain in the right quadrant. There were no noteworthy urinary symptoms. No history of a recent pre-existing skin lesion was obtained.

On admission to the Medical Service of the hospital a diagnosis of subsiding grippe was made, but two weeks after admission it was noted that she had exquisite tenderness in the left costo-vertebral angle and a urologic consultation was requested.

Many urine analyses were made of the non-catheterized bladder specimen, most of them showing only a few white blood cells; many showed the urine to be normal.

When seen by members of the Urological Staff on December 13, 1937, the patient was exceedingly pale and very thin. She had lost quite a good deal of weight. She had marked tenderness in the left costo-vertebral angle and, while no mass could be felt, there was a definite sense of fullness in the left loin. There was no tenderness in the right loin, but the lower pole of the right kidney could be felt. An intravenous urogram suggested marked compression of the left kidney pelvis, and catheterization of the left ureter and retrograde urograms were advised. It was felt that the patient was too sick to prolong the cystoscopy by a similar examination of the right kidney, which had given rise to no symptoms.

On cystoscopy the bladder and ureteral orifices appeared to be normal. Indigo-carmine, injected intravenously, appeared promptly and in quite *deep concentration from both ureters.* The left ureter was readily catheterized, a specimen of urine was collected and a retrograde urogram made. The urine specimen thus obtained showed only two to four white blood cells per high power field. The retrograde pyelogram was similar to the intravenous pyelogram in the chief essentials and emphatically suggested marked compression of the renal pelvis (Fig. 2).

A blood count at this time showed the following: Red blood cells, 2,690,000; hemoglobin, 53 per cent; white blood cells, 17,600; polymorphonuclear cells, 84 per cent.

The temperature was 104 and was of the spiking type. Because of the septic type of temperature, the kidney tenderness, the pyelogram indicating compression, the blood count and the absence of an appreciable amount of pus in the urine, a diagnosis of carbuncle of the kidney was made and immediate operation advised.

On December 14, through an oblique loin incision, the kidney was exposed. The perinephritic fat was very pale. The kidney itself was also very pale and appeared to be somewhat enlarged and quite firm. In the upper half of the kidney on the posterior surface, well up under the ribs, was felt a fluctuating area about the size of a half dollar, and while attempting to separate the upper pole a finger passed

through this area immediately releasing quite a large quantity of yellowish, fairly liquid pus. The cavity whence the pus came was then explored digitally and apparently did not communicate at all with the kidney pelvis. As far as could be estimated, the cavity had held between three and four ounces of pus and its walls were smooth. A large rubber tube drain was led to the opening in the upper pole, a couple of large cigarette drains were placed about the kidney and the wound was closed in layers.

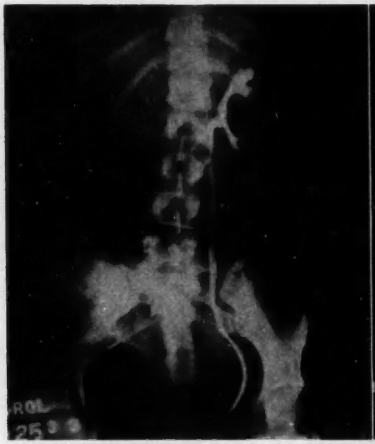


Fig. 2. Case 2. Left pyelogram showing marked compression (by the abscess) of the kidney pelvis.

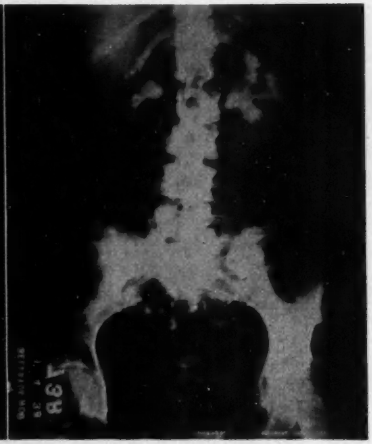


Fig. 3. Case 2. Left pyelogram made three weeks after operation, indicating apparently normal kidney pelvis.

With the assistance of a blood transfusion, the patient began to improve rapidly and made an uneventful recovery.

A blood culture of the pus obtained at the time of operation showed staphylococcus aureus.

The non-protein nitrogen nine days postoperative was 30.

An intravenous urogram made three weeks after the operation indicated a quite normal left renal pelvis (Fig. 3).

Notable among the cases of solitary abscess reported are those of Hunt (1929), Judd and Brown (1929), Beer (1936) and Flandrin (1936).

Beer points out the fact that in the pyelogram, two of the calices may be more widely separated than usual. In Judd and Brown's

case, the pyelogram appeared to be normal, but on close inspection the curve made by the upper ureter and lower border of the pelvis was unusually rounded due to pressure from the large abscess in the lower pole of the kidney. The abscess contained 75 c.c. of thick, yellow, odorless pus, a culture of which revealed the streptococcus hemolyticus and staphylococci. The pyelogram in Flandrin's case was also normal except that the upper calix was pushed somewhat outwards by the large abscess in the upper pole of the kidney. The author did not approximate the size of the abscess but merely referred to the pus released as large in amount, odorless and of greenish color. An examination of the pus showed a pure culture of staphylococcus aureus.

ETIOLOGY AND PATHOLOGY

In most of the reported cases where cultures were made from the pus evacuated from the abscess cavity, the staphylococcus aureus was found in pure culture. In a few instances, however, other organisms were found along with the staphylococcus.

Many of the patients reported gave a history of some pre-existing lesion such as a boil or other type of staphylococcic skin infection. As one would expect, the incidence of such pre-existing infections is seemingly about the same as it is in multiple cortical abscesses, perinephric abscesses and carbuncles of the kidney.

Hunt believes that the large solitary abscess may be the result of extensive coalescence of small embolic abscesses. This may be quite the same view, expressed differently, of other authors who claim that the large solitary abscess is due to the breaking down of the renal carbuncle. Smirnow, however, opposes this theory by stating that kidney carbuncles have no tendency towards suppurative fusion. But whether the large solitary abscess is the result of coalescence of smaller abscesses or breaking down of a carbuncle, or perhaps merely the gradual enlargement of a solitary abscess which begins as a very small one, there can be little doubt that the kidney infection is secondary to another focus of infection, usually a skin infection, wherein coccic emboli or masses of bacteria (cocci) are borne to the kidney by the blood stream and are deposited in the small terminal renal arteries.

The diagnosis of any suppurative parenchymal lesion (not communicating with the kidney pelvis) or any perinephric suppurative

lesion is frequently difficult. The large solitary kidney abscess is no exception to this rule.

A history of boils, carbuncles, paronychia, acute osteomylitis, infected teeth, tonsils or other similar foci of infection, is of the utmost importance in establishing a diagnosis when other signs point to the kidney. In all types of such infections one usually finds chills followed by the spiking type of increased temperature, pain in the loin of the affected side, more or less tenderness about the infected kidney, a moderately high leukocyte count, a low red cell count with a low hemoglobin percentage and finally rather marked loss in weight.

The urinary findings are often negative and therefore frequently misleading. The urine may contain a few white blood cells or staphylococci or both, but at times does not contain either. However, it should be remembered that the suppurative lesions under consideration do not communiacte with the kidney pelvis. Thus, a negative ureteral specimen of urine, considered in connection with the history of a pre-existing skin lesion together with the signs and symptoms indicating renal involvement, should at least arouse one's suspicion as to the true state of affairs rather than confuse the picture.

Frequently, in a fresh specimen of urine staphylococci may be satisfactorily demonstrated by the centrifugal and smear method.

In many instances, kidney functional tests show little or no difference between the functioning capacity of the two kidneys. Hence, diagnostic help from this source cannot always be obtained.

Of considerable aid, however, is the pyelogram. This is especially true in large solitary abscess where the kidney pelvis may be encroached upon by the inflammatory lesion. As mentioned in the foregoing, one looks chiefly for pressure signs such as compression of the pelvis, unusual separation of the calices or displacement of a single calix. The same pyelographic changes may be present in a carbuncle of the kidney, especially if the carbuncle is a large one. But in carbuncle, filling defects of the pelvis seem to be more common, and in many carbuncles there are no significant changes in the pyelogram at all. Also in the differential diagnosis, one must frequently consider perinephric abscess. In this condition the symptoms are likely to be less pronounced and there may be no tenderness in the loin whatsoever. The flat radio-

graph usually shows a curvature of the spinal column (concavity towards the affected side), absence of psoas muscle shadow on the affected side and fixation of the kidney. The pyelogram nearly always shows a normal condition.

TREATMENT

The treatment of large solitary kidney abscess is incision and drainage. On exposure of the kidney in suspected abscess, if the abscess is not at once apparent, decapsulation of the kidneys should be performed, for, as Beer has pointed out, a solitary abscess or multiple abscesses may not be discovered until the true capsule of the kidney is removed.

SUMMARY

Large solitary abscess of the kidney is comparatively rare and is not often diagnosed pre-operatively.

Attention is called to a few of the outstanding cases which have been reported. Two cases of the writer are reported in detail. In one of these the pre- and post-operative pyelograms are very interesting and significant.

The similarity, clinically, of this condition to multiple cortical abscesses, perinephric abscess and carbuncle of the kidney is pointed out.

The treatment of solitary abscess of the kidney is incision and drainage.

REFERENCES

ASCHNER, P. W.: Staphylococcus infection of renal parenchyma. Am. Jour. Med. Sci., 172:63, (July) 1926.

BEER, EDWIN: Coccic infections of renal cortex. Jour. A.M.A., 106:1063, (March 28) 1936.

BRADY, L. J.: Carbuncle of the kidney (metastatic staphylococcus abscess of the kidney cortex)., Jour. Urol., 27:295, 1932.

DICK, B. M.: Staphylococcal suppurative nephritis (carbuncle of kidney). Brit. Jour. Surg., 16:106, 1928.

FLANDRIN, M. P.: Un cas de volumineux abcès du rein à staphylocoques queri par incision et drainage. Bull. de la soc. Française d'urol., pp. 175-184, (April) 1936.

GRAVES, R. C., and PARKINS, L.: Carbuncle of the kidney. Trans. Am. Assn. Genito-Urinary Surgeons, 28:41, 1935.

HUNT, V. C.: Cortical abscess of kidney. Southwestern Med., 13:166, (April) 1929.

JUDD, E. S., and BROWN, C. B.: Cortical abscess of kidney. Surg. Clinics of North America, 9:801, (August) 1929.

KRETSCHMER, H. L.: Carbuncle of the kidney. Jour. Urol., 8:137, 1922.

NEFF, J. H.: Enucleable multilocular abscess (carbuncle) of the kidney. Trans. Am. Assn. Genito-Urinary Surgeons, 23:27, 1930.
O'CONOR, V. J.: Carbuncle of the kidney. Trans. Am. Assn. Genito-Urinary Surgeons, 25:17, 1932.
RESCHKE, K.: Ueber Paranephritis Und Nierenkarbunkel. Arch. f. klin. Chirur., 129:303, 1924.
SMIROW, A. W.: Ueber Nierenkarbunkel. Zeitschr. f. Urol. Chirur., 20:243, 1926.

RETROPERITONEAL TUMOR DISPLACING LEFT KIDNEY

GEORGE R. LIVERMORE, M.D.

Memphis, Tennessee

Retroperitoneal tumors, perineal and juxtarenal, are quite common. Lipomata are the most frequent, but many varieties such as fibrolipomata, lipomyxomata, fibro-lipomyxomata, leiomyomata, fibrosarcomata, liposarcomata, fibro-liposarcomata, myxosarcomata, lipo-myxosarcomata, fibro-lipo-myxoangiosarcomata, lymphangiosarcomata, cystic eptheliomata, rhabdomyomata, et cetera, have been reported. The literature teems with case reports. Crabtree, in 1930, gave us a comprehensive review of the literature and reported a case of perirenal lipoma. In 1936 OcKuly and Douglass reported two cases of perirenal lipomata and again reviewed the literature.

I shall not bore you with the repetition of the extensive literature upon the subject of retroperitioneal tumors, other than to say that most writers seem to be in accord that these growths usually arise in the perirenal fat; but that it is well nigh impossible to determine the origin in many cases, especially as the condition of the patient does not justify the added risk attendant upon the manipulation and time necessary to positively identify the tissue from which the tumor developed. The latter was true in the case which I shall report. The kidney was displaced into the pelvis by the tumor mass, which filled the entire retroperitoneal area from the diaphragm to the pelvic brim. Its enucleation was accomplished piecemeal with rupture of several cysts and much hemorrhage with consequent trauma from the breaking of adhesions, and ligation of bleeding vessels. Therefore, the condition of the patient was so precarious that intravenous glucose in saline, together with adrenalin, coramine and ephedrine, had to be administered, while the pelvic portion of the tumor was being freed and removed. I was thus deprived of the privilege of searching for its point of origin. I believe, however, in view of the displacement of the kidney and the extensive lipomatous tissue in the tumor, we may safely conclude that in this case the tumor had its origin in the

Fig. 1. Framework simulating hypernephroma-the cellular elements having lost their characteristics through degeneration.

Fig. 2. Fibrous tissue.

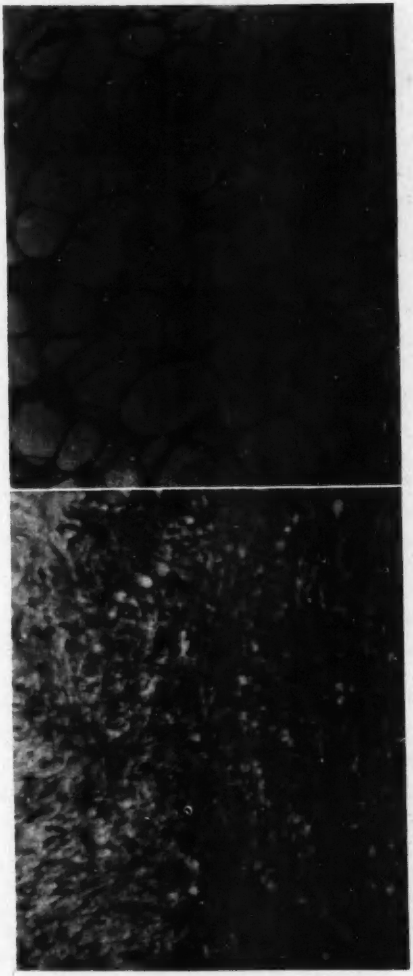


Fig. 4. Fatty tissue.

Fig. 3. Myxoid and connective tissue.

perirenal fat, which later underwent degenerative changes resulting in the mixed character of the growth.

ETIOLOGY

The etiology of these tumors is unknown, although a multiplicity of causes have been suggested. These, as listed by OcKuly and Douglass, include thyroid and pituitary disease, pregnancy, constipation, excessive indulgence in fat-producing foods and alcohol, congenital germinal displacements, inherited tendency to fatness, vasomotor changes and lipomatous degeneration in lymph glands. The patient in the case herewith reported has had chronic pyelonephritis for forty years, with hydronephrosis and dilated and tortuous ureters for at least eight years and perhaps longer. I am wondering if this chronic infection and retention did not play a part in the developement of her tumor. Krogins (quoted by Crabtree) says mesenchymal tissue may be the origin of these growths.

PATHOLOGY

The pathology varies greatly, the lipomata being composed of fat and the fibrolipomata of fibrous tissue and fat that in no wise differs from the normal fatty and fibrous tissue of the body. McConnell, also quoted by Crabtree, reported a large tumor which, like mine, had the characteristics of hypernephroma. It recurred six and a half years after removal. My patient now has a nodule near the lower angle of the scar of her incision that is as large as a man's first. It appeared five months after operation and has gradually increased in size and induration. Lacene, in his description of these tumors, says, "They are generally of considerable volume, always retroperitoneal in all their extent, of varying consistency, flabby and pseudofluctuant at certain points, hard and fibrous at others, of rather regular form, usually multilobed, sunken in furrows, bristling with numerous projections, reddish or yellowish in color, generally slightly vascular of themselves and surrounded by a conjunctive capsule which permits of relatively easy enucleation." The various kinds of tissue found in these tumors has already been stated in the early part of this paper. They may grow to very large proportions. Hirsh and Wells, quoted by Tolson, reported a perirenal liposarcoma weighing 69 pounds, and Crabtree, quoting Young, reports a lipoma of 75 pounds. The

tumor in the case herewith reported weighed 15 pounds, but several large cysts containing about 1,500 c.c. were ruptured during its enucleation, which would make the total weight about 18 pounds. This is quite small in comparison with the case of Young, but as the tumor in my case extended from the diaphragm to the brim of the pelvis and to the right well beyond the midline, it was quite a large growth. Its lightness in weight must be due to the fact that

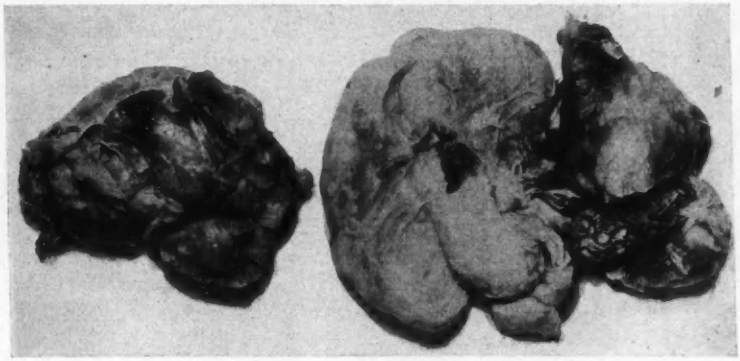


Fig. 5. Retroperitoneal perirenal lipo-fibromyxoma.

the three other types of tissue together with the cysts must have been lighter than fat.

SYMPTOMS

Usually the first symptom is the presence of a mass in the abdomen, usually in the loin, although in some cases the abdomen is uniformly enlarged. These tumors occur most frequently in women. Adams in 113 cases reports 70 per cent in women, and Von Wohlendorf in 165 cases, 72 per cent in women. They occur most frequently after forty (my patient was sixty). Landwers reports a case in a boy fifteen days old and Bork in a girl of one year. They occur with equal frequency in the two sides. There may be slight digestive upsets, weakness, loss of weight and emaciation, even though the growth is not malignant. This is explained by the fact that the fat is not available for tissue economy, the tumor developing at the expense of body nutrition. Pain may or may not be present. In my case it was a prominent symptom,

but the mass was not tender on palpation. Fever is rarely present, but when it occurs it is due to pressure or necrosis. Urinary findings are usually absent, though a rare leukocyte and a few red blood cells may be found. When the presence of the growth causes stasis from misplacement of the kidney or kinking of the ureter, pyelonephritis may result. The blood findings are those of secondary anemia.

DIAGNOSIS

Despite modern diagnostic methods, many of these tumors are not recognized except at operation or autopsy. A diagnosis of hypernephroma of the kidney or an intraperitoneal tumor are the most frequent errors. Cystoscopy, pyelograms, retrograde and intravenous, and plain radiographs should be used in making the diagnosis; but pelvic filling defects and obliteration of the kidney outline by the tumor, may suggest intrarenal, rather than perirenal, tumor. Displacement of a kidney with a normal pyelogram (or, as in my case, abnormalities with which I had been familiar for years) indicates the diagnosis of perirenal, retroperitoneal tumor. In the case herewith reported, the marked displacement of the left kidney by the large tumor mass, which on palpation gave the sensation of a lipoma with moderately indurated areas, justified the diagnosis of retroperitoneal fibrolipoma.

TREATMENT

The treatment of these tumors is removal by operation, followed by deep x-ray therapy if the tumor is malignant. The shock attendant upon the removal of such growths, usually quite large, results in a high mortality which ranges from 20 to 30 per cent. Pemberton and McCaughan of the Mayo Clinic report forty-two cases: seven were not traced; of the remaining thirty-five, twenty-seven died postoperatively within 4.3 years.

The intraperitoneal route is safer, as the mortality is much less than by the transperitoneal approach. Each case, however, is a law unto itself and the urologist must adapt his operation to suit the tumor. It is said that the transperitoneal route is the method of choice in the large tumors that extend into the pelvis and beyond the midline. This may be true in the massive growths weighing from 40 to 70 pounds, but in such cases as the one herewith presented, the retroperitoneal route is not so difficult, unless there

are dense adhesions, which are rare, and planes of cleavage cannot be found. I feel sure the extra shock attendant upon working in the abdominal cavity would have caused the death of my patient had I done a transperitoneal operation. Recurrences are frequent, and cases requiring two and three operations for removal have been reported.

In view of the above and the fact of the rapid recurrence of the growth in my case, I agree with OcKuly and Douglass that postoperative radiation should be included in the treatment of these cases.

CASE REPORT

Mrs. S. F. White, aged sixty, a well developed woman, had been under my care since February 7, 1930, suffering from chronic bilateral pyelonephritis, hydronephrosis, dilated and tortuous ureters. Her family history was of no importance. On her wedding trip forty years ago the patient had an acute pyelitis which became chronic and from which she had continued to have symptoms ever since. In 1915 her right breast was amputated for chronic mastitis and two years later the left one suffered the same fate. She had enjoyed fair health but always suffered with frequent and at times painful urination and nocturia from two to four times. At intervals she would have acute attacks with chills, fever and sweats. She had never been examined cystoscopically until I saw her in February, 1930. In September, 1937, she noted a mass in her left loin and when she came to me I was able to palpate a mass which felt like a lipoma with fibrous areas in her left loin, apparently the left kidney, extending 3 inches below the free border of the ribs. It was not tender but she had pain and a sense of weight in her left side. Cystoscopy and pyelograms showed a mass displacing the left kidney downward and to the right till the pelvis could be seen lying over the promontory of the sacrum. Diagnosis was retroperitoneal tumor, probably fibrolipoma displacing the left kidney downward and to the right into the pelvis.

Upon operation, making the usual oblique kidney incision, a large mass was found in the left kidney fossa extending from the diaphragm nearly to the brim of the pelvis and well to the right of the spine. It was composed of fat, many cysts and fibrous areas. It was easily freed but the cysts ruptured in separating adhesions and a large amount of clear fluid and gelatinous material were evacuated. The sacs were removed together with masses of fat that were lobulated and intermingled with firmer tissue that resembled a myxoma. There was rather free hemorrhage, which was controlled by ligation and packing. The left kidney was found lying low in the pelvis over the promontory of the sacrum. It was pushed up to the left kidney fossa and a gauze pack placed under it. The anesthetist was urging me to

hurry as the patient's condition was alarming, the blood pressure having suddenly fallen from 130/80 to 80/60. I was therefore unable to locate the origin of the tumor, but as the kidney was free of perirenal fat and the mass largely lipomatous, I surmised that it developed in the perirenal fat. Adrenalin, coramine and ephedrine were administered and 1,500 c.c. of 5 per cent glucose in saline were given intravenously while the wound was being closed. The patient left the table with a pulse of 138 and a very weak volume. Blood pressure was 90/60. Digitalis, caffeine and sodium benzoate and external heat were administered, the foot of the bed was elevated, and the patient was typed for transfusion. Six hours later 500 c.c. of blood were given by the citrate method. The patient gradually improved and left the hospital on the eighteenth day with the wound still draining. This was entirely healed on the twenty-sixth day. Five months after operation there was a recurrence of the growth the size of a man's fist at the lower angle of the scar.

Pathologic Report.—The specimen consisted of a large, fatty, nodular mass which was cystic and apparently only partially encapsulated. It weighed 15 pounds. The main portion of the growth was soft, nodular and seemed to be composed almost entirely of fat and myxomatous structure. There was a firm central area which was mottled with areas of dark discoloration suggesting the presence of hypernephroma. There was a large mass of fibrous tissue mixed with fat, and a large amount of old hemorrhage. Frozen section examination from different portions showed a predominance of myxomatous tissue mixed with varying portions of connective tissue and fat. Sections from the firm discolored area above noted showed a framework resembling hypernephroma, the cellular elements having lost their characteristics through degeneration.

Diagnosis.—Lipo-fibromyxoma.

BIBLIOGRAPHY

1. Crabtree, E. Granville: Perirenal lipomata with generalized lipomatosis. Jour. Urol., 33, (May) 1930.
2. Krogins: Quoted by Crabtree.
3. Lacene: French Surg. Congress, 1919.
4. McConnell: Quoted by Crabtree.
5. OcKuly, E. A., and Douglass, Fred M.: Retroperitoneal perirenal lipoma. Jour. Urol., 37, (May) 1937.
6. Tolson, Howard: Perirenal lipoma. Urol. and Cutan. Rev., 40:858, 861, (Dec.) 1936.

DISCUSSION

DR. HUGH CABOT (Rochester, Minn.): I am interested in Dr. Howze's presentation because I feel that it is important to have a more complete identification of the organisms in these cases. I have come to feel that where the proteus is present, prognosis is very importantly altered for the worse. Whether or not the proteus is getting to be a more common weed in this region, I am not clear, but an analysis of a large group of cases that we had at the clinic tended to suggest the proteus did not arrive there by an act of God, but by an act of man, that he was generally put there. We were unable to find any patient with a proteus infection in whom there had never been any instrumentation. I leave the conclusions to be drawn by the experts.

At the present time, as far as we are concerned, we have been unable to abolish proteus once he has become thoroughly settled in his new abode in the kidney. Consequently, it seems to me that you have to approach these cases with this in mind.

One other point I would like to raise here because I am not clear about it, is the question of whether we shall be well advised, given an infection of the kidney with any organism, to institute pre-operative medication. We are all of us aware that these are the cases in which the explosive type of postoperative infection occurs, when on the fourth or fifth day we are faced with the question of whether we shall take out the kidney or whether the pathologist will examine that patient.

In the course of the last year and a half, I have been getting the experts to institute the believed-to-be appropriate method of attack on these organisms. We have had no cases of the explosive type of postoperative infection.

I am particularly interested in Dr. Jeck's paper, because it is a field which I have been exploring a good deal for many years. I am sorry he does not tell us whether a study of the urine by the method suggested by Crabtree in 1910, of very high speed centrifuging for an hour, would or would not have enabled him to spot staphylococcus in the urine. I think they are always present in the early stages. I think they disappear in half the cases within the

first week, but they persist for as much as eight months in some cases.

A recent series of twelve cases in the months from June 1 to July 1, 1937, showed in half those cases from three to eight months after the onset of symptoms, staphylococcus was still obtainable from the urine.

We have found, in the cases in which there was no evidence of perinephritic abscess, that if one explores the perirenal fat, opens the true capsule of the kidney, by just nicking it, and runs his finger around the kidney, he will land on one of these abscesses if it is there, instead of requiring him to free these kidneys, which is not always good for them. I have seen a kidney that when it had been satisfactorily freed, with a central abscess in the mid-portion, was unfortunately separated into two portions and it was not quite clear which, if either, portion one should save or should send to the pathologist for verification of one's very brilliant diagnosis.

Dr. Kretschmer raises with me the question of whether it is necessary also to make a retrograde pyelogram. I think it is, not because we need that conviction, but because we have to show the other fellow. We have to show the internist a really striking change in the normal shape of the kidney. You and I may be satisfied that there is central abscess here from the appearance of the intravenous pyelogram, but, fortunately, as I think, the internist maintains an attitude suggested by the late Charles Elliot, of an abiding skepticism, and for some years we shall have to satisfy that craving of his by retrograde pyelogram.

Dr. George G. Smith (Boston, Mass.): I should like to ask Dr. Cabot whether they have used neoarsphenamine in the later treatment of these long-standing urinary infections. I know there is a great deal of mention of neoarsphenamine in the writings from the Mayo Clinic. I have used it in several of these patients with very striking results. I assume that they have, too, but I wish Dr. Cabot would comment on that.

Dr. Hugh Cabot: In reply to Dr. Smith, I think in the cases in which there is a staphylococcus pyelitis, the chronic type, in which the staphylococcus is either the outstanding organism at the start or after one has skilfully removed the other organisms by

appropriate methods, dear old staphylococcus proves to be the original settler, are often successfully treated by neoarsphenamine.

Within the last year we have been trying neoarsphenamine for the acute and subacute cases of primary renal blood stream infection. I cannot report results except to say that these people have become well and have done better than I expected them to, but that proves nothing.

I believe the method ought to be explored much further. Its very striking effects in the pyelitis which may be secondary to these lesions, but generally is not, is a lead we ought to follow because it is certain that in these blood stream infections of the kidney we have no therapeutics, other than the violence which we like to refer to as surgery.

I think neoarsphenamine shows signs of being useful. I do not think I can go any further.

OBSERVATIONS ON THE ANATOMIC BASIS OF CONGENITAL POLYCYSTIC KIDNEYS

ROBERT F. NORRIS, M.D., and LEON HERMAN, M.D.

From the Ayer Clinical Laboratory and the Urological Service of the Pennsylvania Hospital, Philadelphia, Pennsylvania

Much speculation on the pathogenesis of congenitally polycystic kidneys has not resulted in a definite understanding of the anatomic sequence of events in these cases. Nearly every possible cause or combination of causes has at some time been suggested.

For many years, Virchow insisted that obstruction of the collecting ducts resulted in cystic dilatation of the tubules in the medulla and cortex and was caused by a papillitis. This theory has now been largely abandoned, but French writers especially have continued to believe that syphilis is an important cause of this disease (Favre *et al.*, Bonnamour *et al.*, Delore and Croizat, Banssilon and Guichard, and Lutembacher). By others, the abnormal proliferation of stroma and epithelium in many polycystic kidneys has been interpreted as a true neoplasm (Brigidi and Severi, Nauwerck and Hufschmid). Still others, who have likewise emphasized the importance of the abnormal proliferation of tissue (Herxheimer, McKinley, Cristeller, Rümler), do not believe that a simple failure of union between the collecting ducts and uriniferous tubules proposed as a cause by von Mutach and by Ribbert is an adequate explanation.

Those kidneys, smaller than normal, on the other hand, which have few cysts and epithelial elements usually show atresia of the ureters and apparently are examples of true hypoplasia of renal substance (Rosenow, Baumann).

The most recent important contribution on the subject has been made by Kampmeier. In serial sections of human fetuses of different ages, the earliest generations of uriniferous tubules were found to become detached from the corresponding generations of collecting ducts and were found either to degenerate or become attached to collecting ducts of higher orders. A few were found to remain as cysts for varying periods. It occurred to McKenna and Kampmeier, therefore, that the persistence of an abnormally large number of these tubules as cysts communicating neither with

the pelvis nor with other tubules might readily explain the production of congenital polycystic kidneys.

The association of other congenital anomalies, such as polycystic liver and pancreas, meningocele, polydactylism, et cetera, with polycystic kidneys has frequently been commented upon (Moschcowitz, Sears, Rümler). It is also certain that this condition is

Fig. 1. The enlarged liver is clearly shown. The large masses below are adrenals and kidneys. Compression of the thoracic organs is apparent. (All photographs by Mr. Emil Forney.)

Fig. 3. The great size of the adrenals and kidneys is shown. (From Herman's Urology, 1938, W. B. Saunders and Co.)

hereditary (Bunting, Fuller, Gordon and Trasoff, Schoch) and cystic kidneys have been traced through four or more generations.

The complex nature of the entire problem of etiology and mechanism is thus apparent. Good reviews of the pathogenesis and, in some instances, of the clinical findings in cases of polycystic kidneys may be found in the papers of Busse, Braunwarth, Braasch and Schacht, Bell, Wells, and Puysseleyr.

A full-term male infant, weighing 4,810 grams and measuring 51 centimeters in length, was delivered by extraction of a breech presentation at the Pennsylvania Hospital on February 15, 1937. The mother, aged twenty-five years, had four children, all of whom were well. No history of any familial disease was obtained and there was no history of syphilis in the parents. The blood Wassermann and Kahn tests of the mother were negative. Large abdominal masses

Fig. 2. The biliary ducts show cystic dilatation and intracystic papillary projections.

limited respirations and the child died 20 minutes after birth. Post mortem the blood urea nitrogen was 18.4 mg. per cent.

At necropsy (A. 5717), done two days after death by Dr. T. T. Kochenderfer, the abdomen was greatly distended and measured 42 centimeters in circumference. On section, the liver, adrenals, and kidneys were greatly enlarged (Fig. 1). The cortices of the adrenals were hypertrophied and the lungs were collapsed. No other lesions or congenital anomalies were present and in Warthin-Starry stains of the liver, adrenals, kidneys, and pancreas no spirochetes were demonstrated.

In the liver, which weighed 270 grams, the periportal areas were

widened and the bile-ducts were irregularly dilated into bizarre cyst-like structures lined by cuboidal or flat epithelium. In the lumina papillary projections of loose vascular connective tissue were numerous (Fig. 2). There was no jaundice and no obstruction of the extrahepatic biliary tract. Bile was found in the gall bladder, bile-ducts, and the small intestine.

The kidneys (Fig. 3), weighing together 630 grams, were com-

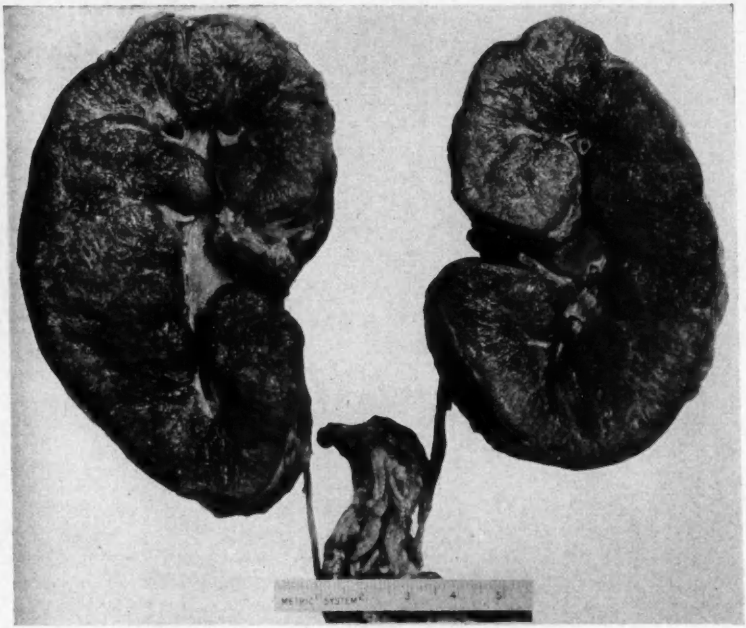


Fig. 4. The kidneys are composed of loose, spongy tissue caused by cystic dilatations of the tubules. In spite of the size the gross architecture is essentially normal and lines of demarcation between cortices and medulla in places are visible. (From Herman's Urology, 1938, W. B. Saunders and Co.)

posed of loose spongy tissue (Fig. 4), the cystic spaces of which averaged about 3 millimeters in diameter. In spite of the size, the gross architecture of the kidneys was generally normal, but the papillæ were small and ill-defined (Fig. 5). The pelves and ureters were patent and normal. The lower genito-urinary tract showed only the characteristics normally found in a full-term infant.

The average distance from papilla to capsule was found to be 1.5 centimeters. A cubic block of tissue having approximately these

dimensions, including a papilla and segments of the medulla and most of the cortex, was taken from each kidney. Serial sections, 15 micra in thickness, were cut at right angles to what is normally the long axis of the papilla. The plane of these sections, therefore, corresponded roughly to that of the capsule. A third block extending from a papilla to the capsule was sectioned serially in a plane at right angles to the others and, therefore, perpendicular to the capsule.

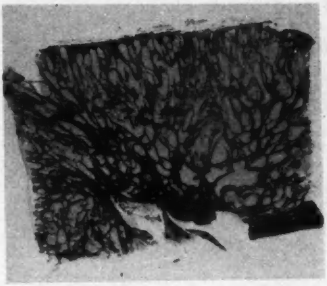


Fig. 5. The papilla is small, irregular, and dense. It is about 1.5 centimeters from the capsule.

In the papillæ, microscopically, were numerous epithelial-lined tubules which were much smaller than the grossly visible cysts, but which were larger than normal tubules. Instead of being densely packed and regular as in the normal kidney (Fig. 6), they were very irregular in outline and diameter and were separated by large amounts of vascular stroma in which were numerous foci of erythropoiesis and myelopoiesis (Fig. 7). Numerous small strands and solid cords of epithelial cells ending blindly in a short distance in either direction were scattered among the patent tubules. From their location and appearance it was certain that the larger tubules were collecting ducts derived from the ureteric anlage. Ten to twelve terminal collecting ducts (Ducts of Bellini) were found to open into each calix. Whether this total represented a reduction in the normal number of sixteen to twenty (Gray) or whether several were overlooked because of the plane of the sections was not determined. On tracing these ducts toward the cortex, some were found to end blindly almost at once without branching. Others, after branching irregularly and asymmetrically, ended blindly some distance from the tip of the papilla. Some were lost at the edge of the block and could not be followed to their termination, but all which could be followed ended blindly. The various branches were thought to represent different orders of collecting ducts and the maximum number of orders of any one duct was found to be seven. If two or three orders are allowed for the

Fig. 6. The regular outlines and the parallel arrangement of the tubules associated with little intervening stroma are shown in the papilla of a normal kidney from a full-term infant.

Fig. 7. The irregularity of the collecting ducts in a papilla of the present case is shown. Large amounts of stroma in which are foci of hematopoiesis separate the tubules.

Fig. 8. A papillary projection of loose vascular stroma extends into the lumen of one of the cystic tubules.

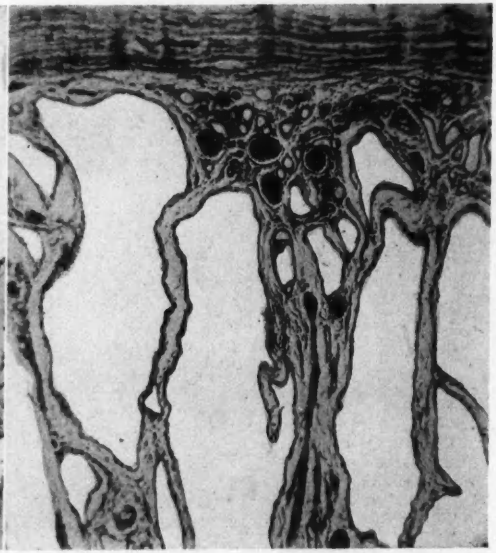


Fig. 9. In contact with the capsule and at right angles to it are large cystic tubules. The arrangement of some resembles that of collecting ducts. Among these cysts are several mature normal glomeruli with no dilatation of the capsules. Collapsed uriniferous tubules are numerous.

Fig. 10. The capsule of a glomerulus deep among the large cysts is dilated.

Fig. 11. A high power photomicrograph of a subcapsular glomerulus in the present case shows its normal development and the blood in the capillary tufts.

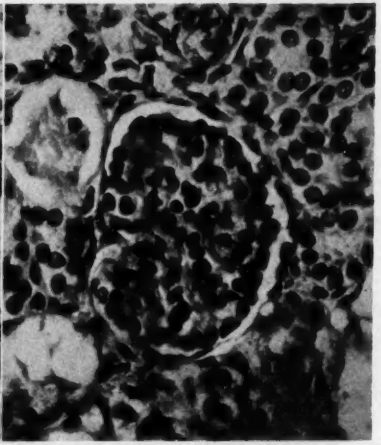


Fig. 12. The normal glomerulus of a full-term infant differs only from that of the present case (Fig. 11) in the greater quantity of blood in the capillary loops.

formation of the calices, the maximum number of orders would be raised to nine or ten.

Between the papillæ and the capsule, the large cysts were irregularly dilated tubules lined usually by a single layer of flattened or cuboidal epithelium. Anastomoses and intercommunications between cysts were numerous and buds ending blindly were strikingly common. Occasionally, however, the epithelium was reduplicated and stratified in no differentiated pattern. In a few of the cysts, definite glomeruli were found and papillary projections of loose vascular tissue in the lumina of some (Fig. 8) might well have been abortive glomeruli. Whether other cysts were derived from collecting ducts could not be determined histologically, but the long axis of many of these cysts was so distinctly at right angles to the capsule (Fig. 9) that such an origin was suggested. Except where these cysts or tubules were continued beyond the edge of the block, all were found to end blindly in the cortex and none communicated directly or indirectly with the calix. Compared to that of the papillæ, the stroma was scanty and loosely arranged and appeared no more vascular than normal.

Among the dilated tubules and cysts in the medulla and deeper portions of the cortex were only a few glomeruli. Some of these were scarred and obliterated. In the case of others, the capsules of Bowman and short uriniferous tubules ending blindly were dilated (Fig. 10). In the subcapsular region, however, were many glomeruli which were not only mature but were also normally formed (Fig. 9). No neogenic zone was present. The capillaries in the glomerular tufts contained blood (Fig. 11), but were not so dilated as the capillaries of those in a normal full-term infant (Fig. 12). Arising from these capsules of Bowman, which were collapsed, were short blindly ending uriniferous tubules without lumina. The cells of these tubules, however, were pink-staining and columnar and resembled those of the normal convoluted tubules.

In order to demonstrate these abnormalities more clearly, drawings to scale of several of the collecting ducts emptying into a calix and several of the dilated cysts above were reconstructed. Since the subcapsular glomeruli and the attached tubules were so normally formed, reproduction of these was thought to be unnecessary. Reconstructions were accomplished by projecting images of serial sections on graph paper at such a magnification that the actual thickness of the sections, 15 micra, was equal to the ruling of one-tenth inch on the graph paper. Tracings of these images were measured and transferred to a single sheet of graph paper. Diagrams accurate in two dimensions were thus made. By taking into account the measurements of the unplotted third dimensions, the artist, Mr. William Brown McNett, was able to reconstruct the collecting ducts and cysts shown in Figure 13.

In wax-plate reconstructions of tubules and cysts from cystic kidneys somewhat similar to those of the present case, Meader, then

Fig. 13. The blindly ending collecting ducts communicate with a calix. The irregularity, budding, asymmetrical branching, and distortion are shown. Small cysts are probably segments of former tubules or ducts. The large cyst-complex above shows several cystic tubules with buds and anastomosing branches without definite pattern. The anterior portions of several tubules are omitted to show the posterior anastomoses. A collecting duct and cystic tubule extend without terminating beyond the edge of the block. The approximate vertical extent of this illustration in the actual kidney was 0.63 cm.

Forssman, and finally Greene found normal glomeruli with short uriniferous tubules emptying into large blindly dilated cysts. Greene found many intercommunications between these cysts and thought that the second portion of the proximal convoluted tubule first became dilated. Meader also found that some glomeruli were associated with short collapsed tubules which ended blindly and that many of the larger cysts had no traces of glomeruli. Forssman believed that some

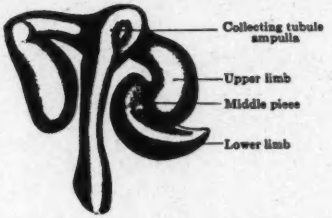


Fig. 14. The S-shaped anlagen of the glomeruli and uriniferous tubules are shown uniting with the collecting ducts. (From Kiebel and Mall's Human Embryology, 1912, J. B. Lippincott Company.)

of the cysts were formed from pinched-off segments of collecting ducts. In general, therefore, the reconstructions of others agree with ours except that in the present case no undilated tubules were seen to enter the cysts.

A discussion of these abnormal findings depends in part on an understanding of the normal development of the kidney. It will be recalled that normally the ureter grows cephalad from the Wolffian duct to meet the nephrogenic substance which is the anlage of the glomeruli and the secretory or uriniferous tubules. The expanded distal end of the ureter forms the pelvis of the kidney from which sprout collecting ducts of successive generations. The first two or three generations enter into the formation of the calices and papillæ. The end-buds, however, are capped from the first by the nephrogenic tissue. There is some question whether or not glomeruli and uriniferous tubules are elaborated before the fourth generation of collecting ducts. Beginning with the fourth or fifth generation, at any rate, collections of cells from the nephrogenic substance become concentrated about the blind ends of the ducts to form the metanephric spheres and vesicles. The lumina of these future capsules of Bowman connect with those of the collecting ducts by short S-shaped anlagen (Fig. 14). These anlagen develop into the proximal and distal convoluted tubules with the interposed loops of Henle. Some twelve generations of collecting ducts with attached glomeruli and uriniferous tubules are thus formed. The oldest generations of glomeruli are nearest the pelvis, the youngest are subcapsular.

Of the possible anatomic explanations in the present case, therefore, two seem most likely. First, the distorted and atypical collecting ducts in the papillæ for some reason may have failed to join the developing uriniferous elements. Having no outlet the latter became cystic and enlarged with accumulated secretion. The presence of glomerular tufts in an occasional cyst is proof that some of them were derived from uriniferous elements. Since the isolated normal

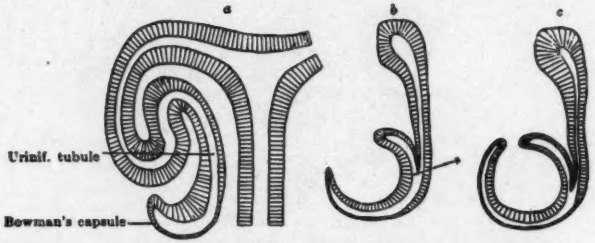


Fig. 15. The lumina of the S-shaped anlage and the developing capsules of Bowman are seen to be continuous with those of the collecting ducts. (From Kiebel and Mall's Human Embryology, 1912, J. B. Lippincott Company.)

glomeruli in the subcapsular region were much younger than those in the deeper portions, according to such a hypothesis, time had not yet elapsed for them to become dilated into cysts. This explanation would be consistent with the simple nonunion theory of Ribbert and others.

The presence of isolated normal and mature glomeruli, ending blindly without dilatations of the capsules, at the extreme periphery of the kidney is difficult to explain on such a basis, however, because normally differentiation of the glomerulus is not complete until after continuity of the lumina of the collecting duct and capsule of Bowman is established (Keibel and Mall, Fig. 15). No such continuity of lumina with any structure was observed in any of the normal peripheral glomeruli studied. Although under certain abnormal conditions in embryos of mice (Brown) and in tissue cultures of chick embryos (Seevers) the nephrogenic tissue will apparently differentiate into rudimentary tubular structures in the presence of a ureter without actual union with collecting ducts, the differentiation of the nephrogenic blastema into metanephric spheres, vesicles, and finally glomeruli is so intimately associated with the end-bud of the growing collecting ducts (Huber, Keibel and Mall) that it is difficult to understand how such anatomically normal glomeruli could develop one centimeter away from the nearest collecting duct. There is, furthermore, no apparent anatomical reason in the present case why such a failure of union occurred. The lack of inflammation at the time

of death is not of itself important, but the absence of scarring indicates that a former inflammation sufficiently extensive to prevent union did not occur. The parallel arrangement of many of the cysts at right angles to the capsule (Fig. 9) suggests, moreover, that some of them may not be uriniferous tubules but may be derived from collecting ducts. Although the potentialities of embryonic tissue are great, the tendency of the larger cysts to bud and to anastomose with others is more in keeping with the activity of collecting ducts than that of uriniferous tubules.

These objections suggest a second explanation. Up to a certain period in fetal life, development with union of the collecting ducts and uriniferous tubules occurred more or less normally. Instead of remaining normal, degeneration of the tubules and collecting ducts then occurred with dissociation of cystic segments. Proliferation of these segments may or may not have continued. The peripheral normal glomeruli, likewise, were so recently detached as not to have become cystic or may have become detached from segments already cystic.

It will be noted in Figure 4 that the gross architecture of the kidneys is practically normal. Not only are the primary lobulations well-defined, but close inspection reveals secondary indentations. The latter may well represent the presence of former secondary columns of Bertini. The cortex can frequently be distinguished from the medulla and in places suggestions of medullary rays are seen. The calices and pelves are not deformed. It is manifestly difficult from these observations to determine whether development of the kidneys was at first normal and, if so, at what age normal development ceased. Such a normal gross architecture, however, would hardly result if the stunted and atypical collecting ducts did not at any time extend beyond the small papillary areas. The gross structure of the liver in the present case furthermore was also not abnormal. In serial sections of two blocks, a great distortion of the bile ducts into cystic dilatations was found but no actual obstruction of any of them was demonstrated.

It has been proposed that an overproduction of excretory elements occurs and that reduction in the number takes place in the normal kidney. Persistence of these glomeruli and tubules would explain the occurrence of polycystic kidneys (Teuscher). A similar but more complex mechanism was suggested by Keibel and Mall and later by Kampmeier that early generations of uriniferous tubules and their glomeruli normally become detached from the collecting ducts and join collecting ducts of higher orders. Kampmeier also believed that an early overproduction of uriniferous elements is followed by a degeneration and reduction in the numbers of these elements. In normal fetuses some of these tubules may remain temporarily as small cysts. The persistence of large numbers of these cysts, therefore, would explain the occurrence of polycystic kidneys. Although no such migration or cystic degeneration of uriniferous tubules has been

Fig. 16. The cyst-like capsules of Bowman in the mesonephros are connected with the Wolffian duct by short tubules.

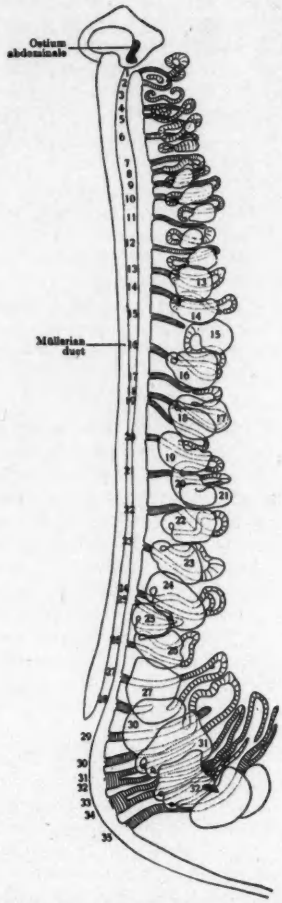


Fig. 17. In the degenerating mesonephros, isolated capsules of Bowman and segments of tubules as well as anastomoses between tubules are shown.

(From Kiebel and Mall's Human Embryology, 1912, J. B. Lippincott Company.)

observed in chick embryos (Rienhoff, Warner), it is possible that some of the cysts near the calices in the present case may have had such an origin. On the other hand, if all the cysts in the present case were derived from uriniferous tubules, the presence of subcapsular normal but detached glomeruli and tubules is just as difficult to explain as in the case of the simple nonunion theory.

That degeneration of the epithelial elements in polycystic kidneys may occur has been previously stated (Forssman). Precedent for a cystic type of degeneration can also be found in the case of the mesonephros and it has even been proposed that persistence of the mesonephros in association with the metanephros might explain the occurrence of polycystic kidneys (Still, Baccarini). In Keibel and Mall, one can readily observe from diagrams of their reconstructions (Figs. 16 and 17) that the capsules of Bowman are normally dilated and it is claimed that they become more cystic during degeneration. As degeneration of the mesonephros proceeds, the capsules and glomeruli may become detached; segments of tubules and ducts may become isolated; and some of them may actually anastomose with others. All of these changes were present in this case (Figs. 9, 10 and 13).

From the evidence we favor, therefore, the second mode of origin, namely, that up to a certain period in fetal life development of the kidneys was normal; that by degeneration glomeruli and segments of tubules and collecting ducts became cystic and isolated; and that the continued growth of these cysts caused the great increase in the size of the kidneys. Definite conclusions should not be drawn, however, from a study of one case of polycystic kidneys and from the reconstruction of only a few collecting ducts and cysts. More reconstructions are necessary before any definite anatomic pattern can be established. An adequate explanation of polycystic kidneys must satisfactorily account for the associated congenital anomalies and the hereditary nature of the disease. As has been previously suggested (Sears, Teuscher, Gridnev), therefore, the ultimate cause of congenital polycystic kidneys should be searched for in the germ plasm.

SUMMARY

1. A case of congenital polycystic kidneys in a new-born infant is described.

2. From serial sections several collecting ducts and cysts have been reconstructed to scale in a drawing.

3. The kidneys can be divided roughly into three zones. In the papillæ, atypical collecting ducts communicated with the calices but not with the cysts. The middle zone was composed of dilated branched tubules among which were numerous anastomoses. In the subcapsular zone were numerous normal mature glomeruli with

short uriniferous tubules which were not dilated and which ended blindly.

4. The most plausible explanations of these findings are discussed and it is suggested that up to a certain period in fetal life development of the kidneys was normal. Degeneration and cystic changes resulted in dissociation of the nephrons into segments. The continued proliferation of these segments and the retention of secretory products caused the cyst-like dilatation of the tubules and the enlargement of the kidneys.

5. The ultimate cause of congenital polycystic kidneys will be found in the germ plasm.

REFERENCES

BACCARINI, L.: Arch. ital. d. Chir., 26:618, 1930.
BANSSILON and GUICHARD: Bull. d. Soc. d'Obst. et d. Gynéc. d. Paris, 22:415, 1933.
BAUMANN, R.: Virch. Arch. f. path. Anat., 281:846, 1931.
BELL, E. T.: Am. Jour. Path., 11:373, 1935.
BONNAMOUR, DOUBROW, and NAUSSAC: Lyon Méd., 140:368, 1927.
BRAASCH, W. F., and SCHACHT, F. W.: Surg., Gynec. and Obstet., 57:467, 1933.
BRAUNWARTH, C.: Virch. Arch. f. path. Anat., 186:341, 1906.
BRIGIDI, D. V., and SEVERI, A.: Lo Sperimentale, 46:1, 1880.
BROWN, A. L.: Am. Jour. Anat., 47:117, 1931.
BUNTING, C. H.: Jour. Exper. Med., 8:271, 1906.
BUSSE, O.: Virch. Arch. f. path. Anat., 175:442, 1904.
CRISTELLER, E.: Med. Klin., 23:1447, 1927.
DELORE, P., and CROIZAT: Arch. Franco-Belges d. Chir., 31:177, 1928.
DELORE, P., and CROIZAT: Rinasc. med., 6:158, 1929.
FAVRE, BONNAMOUR, DOUBROW, and BOUYSSET: Compt. rend. Soc. d. biol., 95:471, 1926.
FORSSMAN, J.: Beitr. z. path. Anat. u. z. allg. Path., 56:500, 1913.
FULLER, C. J.: Quart. Jour. Med., 22:567, 1928-29.
GORDON, G. R., and TRASOFF, A.: Am. Jour. Med. Sc., 194:112, 1937.
GRAY, H.: Anatomy of the Human Body. Twenty-second Edit. Philadelphia: Lea and Febiger, 1930.
GREENE, C. H.: Am. Jour. Dis. Children, 24:1, 1922.
GRIDNEV, A.: Ztschr. f. urol. Chir., 34:47, 1932.
HERXHEIMER, G.: Virch. Arch. f. path. Anat., 185:52, 1906.
HUBER, G. C.: Am. Jour. Anat., 4: Supplement, 1905.
KAMPMEIER, O. F.: Arch. f. Anat. u. Physiol., Anat. Abteil: 204, 1919.
KAMPMEIER, O. F.: Surg., Gynec. and Obstet., 36:208, 1923.
KAMPMEIER, O. F.: Ztschr. f. Gesamte Anat., 1 Abteil., 73:459, 1924.
KAMPMEIER, O. F.: Anat. Rec., 33:115, 1926.
KEIBEL, F., and MALL, F. P.: Manual of Human Embryology, Vol. 2. Philadelphia: J. B. Lippincott and Co., 1912.
LUTEMBACHER, R.: Ann. d. Méd., 39:440, 1936.
MCKENNA, C. M., and KAMPMEIER, O. F.: Jour. Urol., 32:37, 1934.
MCKINLEY, C. A.: Jour. Urol., 4:195, 1920.
MEADER, F. M.: Bull. Johns Hopkins Hosp., 18:354, 1907.
MUTACH, A. VON: Virch. Arch. f. path. Anat., 142:46, 1895.
MOSCHCOWITZ, E.: Am. Jour. Med. Sc., 131:674, 1906.
NAUWERCK, C., and HUFSCHMID, K.: Beitr. z. path. Anat. u. z. allg. Path., 12:1, 1893.

PUYSSELEYR, R. DE: Jour. d'Urol., 41:201, 1936.
RIBBERT, H.: Verhandl. deutsch. path. Gesellsch., 2:187, 1899.
RIENHOFF, JR., W. F.: Bull. Johns Hopkins Hosp., 33:392, 1922.
ROSENOW, G.: Virch. Arch. f. path. Anat., 205:318, 1911.
RÜMLER, E.: Virch. Arch. f. path. Anat., 292:151, 1934.
SCHOCH, H.: Schweiz. Med. Wchnschr., 28:652, 1937.
SEARS, W. G.: Guy's Hosp. Reports, 6:31, 1926.
SEEVERS, C. H.: Anat. Rec., 54:217, 1932.
STILL, G. F.: Trans. Path. Soc. of London, 49:155, 1897-98.
TEUSCHER, M.: Beitr. z. path. Anat. u. z. allg. Path., 75:457, 1926.
WARNER, F. J.: Anat. Rec., 36:271, 1927.
WELLS, C.: Brit. Jour. Urol., 8:22, 1936.
VIRCHOW, R.: Virch. Archiv. f. path. Anat., 46:506, 1869.
VIRCHOW, R.: Berlin Klin. Wchnschr., 29:104, 1892.

THE ASSOCIATION OF POLYCYSTIC DISEASE OF THE KIDNEYS WITH CONGENITAL ANEURYSMS OF THE CEREBRAL ARTERIES

C. R. O'CROWLEY, M.D., and HARRISON S. MARTLAND, M.D.

From the Departments of Urology and Pathology of the Newark City Hospital, and the Office of the Chief Medical Examiner of Essex County, Newark, New Jersey

Polycystic disease of the kidney has occupied a prominent and interesting place in both the urologic and general medical literature of the past quarter of a century. During this period there have been great differences of opinion as to the etiology of the cystic kidney. It is generally believed that the cysts are retention cysts and depend upon obstruction at some point along the course of the uriniferous tubule.

The original theory of Virchow that kidney cysts were the outcome of an embryonal or fetal nephritis which caused a fibrosing papillitis, has been abandoned in favor of a theory based purely on developmental defects. The exact site and nature of the developmental fault, however, is still a matter of dispute.

Most investigators agree that kidney cysts arise from a failure of proper fusion of the secretory and excretory systems (collecting tubules) during the embryonic formation of the kidney. This is a lack of union between the derivatives of the mesodermal nephrogenic cord and the ureteric buds. Oertel[8] states that incomplete convoluted tubules and loops, actual misdirection in the differentiation of the nephrogenic cell masses, abnormal mesodermal derivatives (muscular and mucoid tissue), abortive abbreviated ureteric buds, adenomatous growths, et cetera—all have been found in polycystic kidneys. He further also states:

> "The question whether there exist fundamental genetic differences in the formation of solitary cysts and the genuine polycystic kidney has been denied by the majority of investigators, who recognize only quantitative differences in these respects. On the other hand, some still emphasize the possibility of certain distinctions in the origin of these two types."

Kampmeier[7] claims that this condition is caused by cystic atrophy of the first generation of excretory tubules, that these, in-

stead of being lost, persist, and thus prevent the formation of new functional collecting tubules.

However, despite these and many other controversial opinions, pathologists and urologists are today agreed that the polycystic kidney is congenital, developmental in origin and always bilateral.

The purpose of this paper is to add evidence for the theory of the congenital etiology of the polycystic kidney, by presenting the

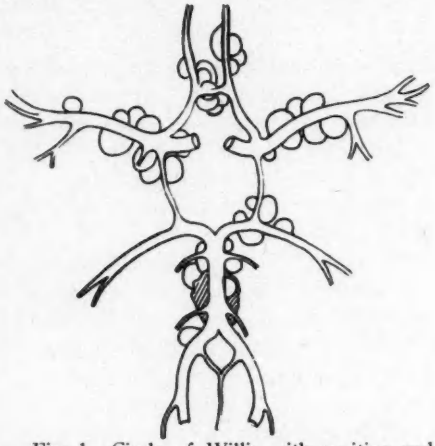


Fig. 1. Circle of Willis with position and relative size of thirty-eight congenital "berry" aneurysms found at autopsy in fifty-four cases of spontaneous subarachnoid hemorrhage. A larger aneurysm (shaded) on the basilar artery due to arteriosclerosis is also shown.

association of this condition with other congenital defects. Of greatest importance is the simultaneous occurrence of spontaneous subarachnoid hemorrhage caused by rupture of congenital "berry" aneurysms of the vessels of the base of the brain.

One of us (M.), as Chief Medical Examiner of Essex County (Newark), N. J., has observed fifty-four cases of spontaneous subarachnoid hemorrhage in a series of more than 10,000 routine medico-legal autopsies performed during the past twelve years. In thirty-eight of these fifty-four cases a ruptured, congenital, berry aneurysm of the circle of Willis, at or near the bifurcation of its larger branches, was found.

In seven of these instances in which a congenital aneurysm of the cerebral vessels was demonstrated, there were other associated congenital defects. Three showed large, bilateral, polycystic kidneys (two of these cases also had aberrant bile duct cysts of the liver) whereas four further cases revealed minor congenital defects—hypoplasia of left kidney; stenosis of abdominal aorta with hypoplasia of left kidney; and the presence of a Chiari's network in the right auricle; and finally a case showing abnormal position of both adrenals.

This illustrates the well recognized fact that congenital lesions, often of widely varying character, may frequently be found to occur simultaneously. Many instances in the literature illustrate the occurrence of two, and often multiple, defects in the same individual.

However, although we have found no specific reports in the literature per se of the simultaneous occurrence of polycystic kidneys and congenital cerebral aneurysms, a careful study of the literature reveals two such instances reported along with other congenital defects. The first such case was reported by Dunger in 1904.[3] This worker reports a father, son and nephew who had polycystic kidneys; the son died of an aneurysm of the middle cerebral artery. In 1905 Sieber[9] reports 212 cases of polycystic kidneys. Ten of these patients died of cerebral hemorrhage, yet no berry aneurysms were observed, and the deaths were regarded as ordinary apoplexies, resulting from the hypertension so frequently associated with late polycystic disease of the kidneys.

In 1909, Coombs,[3] reported five deaths from cerebral hemorrhage in forty-two cases of polycystic disease of the kidneys. From autopsy reports, however, none of these could be identified with certainty as due to ruptured cerebral aneurysms of congenital origin; six appeared to have been caused by arteriosclerotic changes.

Fearnsides,[5] in 1916, reported thirty-one cases of congenital cerebral aneurysms. In but seven of these were complete autopsies performed. In one case, the patient died of renal insufficiency due to congenital, bilateral polycystic disease of the kidneys. Autopsy revealed two small unruptured berry aneurysms; one at the junction of the left anterior cerebral and anterior communicating arteries, the other on the right middle cerebral artery. These were but incidental autopsy findings.

Katz and Müehe,[6] in 1924, reported a case of a woman who had suffered from severe headaches since childhood and died suddenly at the age of forty-five. At autopsy a ruptured aneurysm of the anterior communicating artery, and a second unruptured aneurysm at the junction of the internal carotid and right middle cerebral arteries were found in association with congenital bilateral polycystic kidneys.

Fig. 2. Case 1. Brain showing spontaneous subarachnoid hemorrhage due to ruptured congenital aneurysm on right middle cerebral artery. Two unruptured aneurysms may be noted on the left middle cerebral artery.

It may be said in summary, therefore, that of ninety cases of congenital cerebral aneurysms reported (in thirty papers) in the literature in which adequate autopsy protocols are available, there were found only two cases of bilateral congenital polycystic disease of the kidneys associated with spontaneous subarachnoid hemorrhage.

There are a large variety of other congenital defects which

have been reported in association with congenital polycystic disease of the kidneys. Although most of these are of minor importance, gross defects, especially in the stillborn, showing extensive cystic disease of the kidneys and liver, are encountered. These defects occasionally interfere with the mechanism of labor.

Clinicians recognize that bilateral polycystic disease of the kidneys may exist throughout most of early adult life as an unsuspected condition. In most instances these individuals gradually develop renal insufficiency, which sooner or later leads to renal hypertension and secondary atheromatous changes in the cerebral and coronary arteries. Except for occasional renal hemorrhage or symptoms produced by pressure the first evidence of the presence of this disease is often manifested by renal insufficiency, uremia, coma and death. Thus, such individuals often live to the fourth and fifth decade before symptoms of the disease present themselves. In some cases, however, because of the hypertension and associated blood vessel changes, death may result from cerebral hemorrhage or from coronary disease and its sequellæ, rather than from uremia.

Many such cerebral deaths would be diagnosed clinically as ordinary apoplexy. Unless confirmed by autopsy the accuracy of this diagnosis can never be proven, since some may be due to rupture of congenital aneurysms. Thus, when a cerebral hemorrhage occurs in an individual known to have congenital polycystic kidneys the possibility of subarachnoid hemorrhage due to associated defects in the cerebral arteries of congenital origin must be seriously considered.

A review of the literature has revealed but two instances of death from subarachnoid hemorrhage caused by congenital cerebral aneurysms in which the autopsy also disclosed bilateral polycystic disease of the kidneys (Cases of Dunger, Katz and Müehe, quoted above).

In the present series of fifty-four cases of spontaneous subarachnoid hemorrhage, in thirty-eight the bleeding was definitely caused by rupture of congenital berry aneurysms of the circle of Willis, or its larger branches. Of these thirty-eight cases, congenital, bilateral polycystic disease of the kidneys was found at autopsy in three instances. Since it is not unusual to observe two or more congenital defects in the same individual, the association

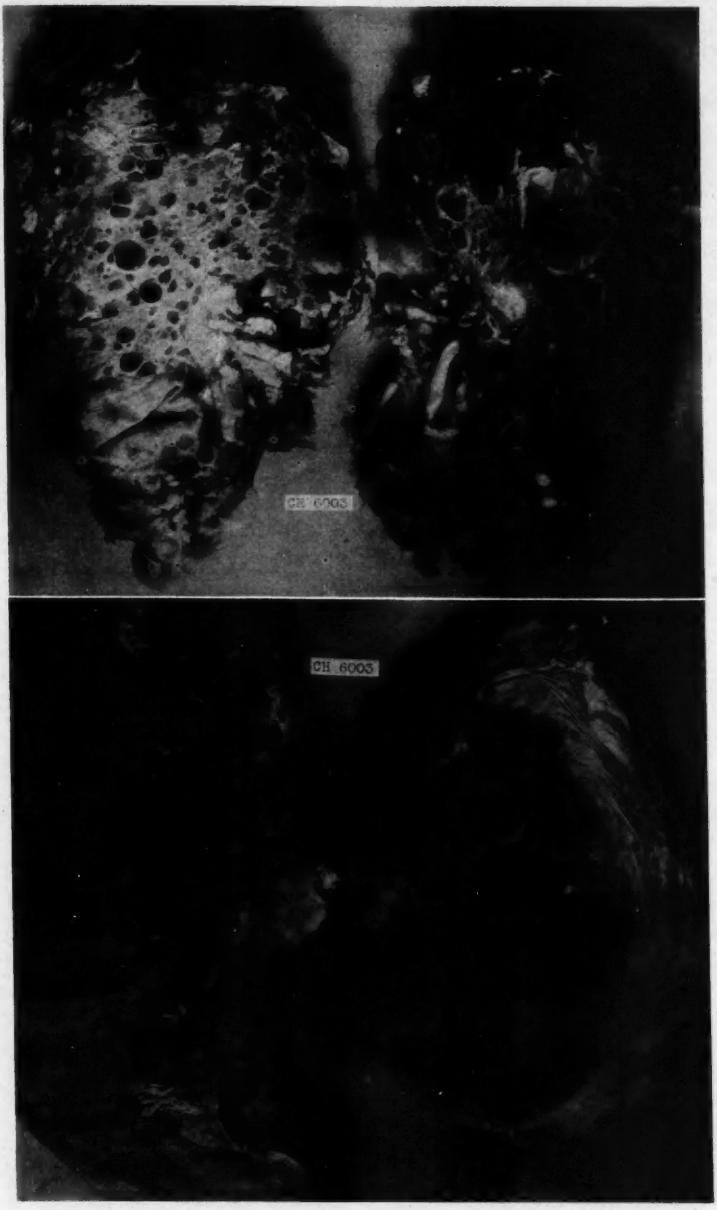


Fig. 3. *(above)* Case 1. Congenital bilateral polycystic disease of the kidneys. The left kidney weighed 480 grams, the right kidney 490 grams.
Fig. 4. *(below)* Case 1. Liver showing extensive congenital aberrant bile duct cysts.

of polycystic kidneys and berry aneurysms in the same individual is evidence for the congenital origin of both conditions.

REPORT OF CASES

Case 1.—Ruptured congenital berry aneurysm of right middle cerebral artery with spontaneous subarachnoid hemorrhage. Bilateral, congenital, polycystic disease of kidneys. Extensive aberrant bile duct cysts of liver. Congenital cyst of spleen. Unruptured berry aneurysm of left middle cerebral artery. No arteriosclerosis or syphilis.

The patient, a white man, forty-two years of age, complained of frequent headaches and vertigo. He was suddenly seized with severe headache followed by unconsciousness and convulsions. On admission to the hospital he was in deep coma. The spinal fluid which at this time contained blood, later became zanthochromic. He remained in deep coma until four days later when death occurred. Clinical diagnosis: Spontaneous subarachnoid hemorrhage.

Necropsy.—Height 5 feet, 8 inches, weight 160 pounds

Brain—There was extensive subarachnoid hemorrhage over the inferior and lateral surfaces of the right frontal lobe; secondary rupture into the subdural space and brain parenchyma with intracerebral clot 5 cm. in diameter; compression of right lateral ventricle and flattening of convolutions over superior surface of brain. Ruptured, lobulated, berry aneurysm of right middle cerebral artery 2.5 cm. from origin of this vessel. Aneurysm was 1 cm. in diameter, within Sylvian fissure, rupture of superior surface of aneurysm. Two unruptured berry aneurysms, each 4 mms. in diameter, were found on the left middle cerebral artery.

Kidneys—The left kidney measured 14 x 9 x 5 cm. and weighed 480 grams. Most of the kidney parenchyma was replaced by numerous cysts, ranging in size from those just visible to larger ones 1 cm. in diameter. Most cysts contained clear serous fluid, others opalescent, cloudy fluid. Right kidney measured 15 x 7 x 6 cm. and weighed 490 grams; same general appearance and detail as left kidney.

Liver was markedly enlarged and weighed 3,100 grams. Both lobes contained innumerable cysts, varying in size from 1 mm. to 4 cm. Cysts contained watery or light yellowish fluid and were lined by smooth, glistening membrane.

Spleen was normal in size and contained a solitary cyst 1.5 cm. in diameter. There was no hypertrophy of the left ventricle, no evidence of syphilis or arteriosclerosis except for an occasional yellow streak of atheroma in the aorta.

Case 2.—Ruptured congenital berry aneurysm of anterior communicating artery with spontaneous subarachnoid hemorrhage. Bilateral, congenital, polycystic disease of kidneys. Aberrant bile duct

cyst of liver. Surgical decompression. Obesity. No arteriosclerosis or syphilis.

The patient, a white woman, fifty-six years of age, was found on the floor of the bathroom where she had apparently fallen, receiving laceration of the scalp. She was admitted to the hospital in coma, with stiff neck, fever and high blood pressure. Spinal fluid was bloody. Diagnosis of possible traumatic cerebral hemorrhage was made and a left temporal decompression performed. The patient lived three days.

Necropsy.—Weight 210 pounds.

Brain—There was extensive subarachnoid hemorrhage over the inferior surface of both frontal lobes, extending over the base of the brain and lateral surfaces. Ruptured berry aneurysm, 8 mm. in diameter, was found on the anterior communicating artery near the left anterior cerebral. There was secondary intracerebral hemorrhage in the left frontal lobe breaking into the anterior horn of the left lateral ventricle, with extensive interventricular hemorrhage.

Kidneys.—The left kidney measured 17 x 10 x 8 cm. and weighed 600 grams. It was the seat of innumerable small and large cysts, containing clear serous fluid and yellowish and brownish fluid forming a display of color in the cut section of the kidney. Very little kidney parenchyma was recognizable. The right kidney measured 15 x 9 x 6 cm., weighed 510 grams, and had the same general appearance as the left kidney.

Liver showed one aberrant bile duct cyst 3 cm. in diameter. The rest of the autopsy revealed essentially negative findings except for obesity and recent surgical decompression. There was no hypertrophy of the left ventricle and no evidence of syphilis or arteriosclerosis.

Case 3.—Ruptured congenital berry aneurysm of right middle cerebral artery with spontaneous subarachnoid hemorrhage and secondary hemorrhage in lateral ventricle and subdural space. Congenital polycystic disease of kidneys. No arteriosclerosis or syphilis.

The patient, a white man, twenty-seven years of age, had a sudden onset of severe headache followed by restlessness, tenderness and rigidity in the neck, and unconsciousness. He was admitted to the hospital where he remained in deep coma and died two and one-half days later.

Necropsy.—Height, 5 feet, 11 inches; weight, 180 pounds.

Brain.—There was extensive subarachnoid hemorrhage over the inferior surface of the right frontal and temperosphenoidal lobes extending over the base and the lateral surfaces of the brain. Ruptured berry aneurysm, 3 mms. in diameter, was found on the right middle cerebral artery near the junction of the internal carotid. There was

secondary hemorrhage into the cerebrum breaking into the right lateral ventricle and into the right subdural space.

Kidneys.—The left kidney measured 19 x 9 x 7 cm. and weighed 650 grams. The whole kidney was the seat of extensive small and large cysts. There was very little recognizable kidney parenchyma. The right kidney measured 21 x 10 x 8 cm. and weighed 800 grams, and had the same appearance as the left.

There was no hypertrophy of the left ventricle, no evidence of syphilis or arteriosclerosis, except for an occasional patch of soft atheroma in aorta and coronary arteries.

OTHER CONGENITAL DEFECTS ASSOCIATED WITH CONGENITAL ANEURYSMS OF THE CEREBRAL ARTERIES

Congenital Hypoplasia of Kidney.—In this series of fifty-four cases of spontaneous subarachnoid hemorrhage in which a congenital aneurysm was the source of the bleeding in thirty-eight instances, a congenital hypoplasia of the kidney was observed twice.

Case 1.—Ruptured congenital berry aneurysm of right middle cerebral artery with spontaneous subarachnoid hemorrhage and secondary hemorrhage into brain parenchyma and subdural space. Congenital hypoplasia of left kidney. Congenital stenosis of abdominal aorta. Compensatory hypertrophy of right kidney.

A white man, twenty years of age, fell while at work in a chemical dye plant. He had convulsions followed by unconsciousness, and died five minutes after admission to the hospital.

Necropsy.—Height, 5 feet, 8 inches; weight, 140 pounds.

There was extensive spontaneous subarachnoid hemorrhage over the base of the brain with secondary hemorrhage in the right temperosphenoidal lobe and subdural space. Ruptured berry aneurysm, 1 cm. in diameter, was found on the right middle cerebral artery. An unruptured aneurysm, 0.5 cm. in diameter, was found on the left vertebral artery.

There was congenital hypolasia of the left kidney; miniature kidney with fetal lobulations well retained. The ureter was patent. Congenital stenosis of the abdominal aorta, admitting only the tip of the finger, opposite the left renal artery. Compensatory hypertrophy of right kidney.

Case 2.—Ruptured congenital berry aneurysm of left vertebral artery with spontaneous subarachnoid hemorrhage. Congenital hypoplasia of left kidney with compensatory hypertrophy of right kidney.

A white man, forty years of age, was found dead in an automobile.

Necropsy.—Height, 5 feet, 7 inches; weight 135 pounds.

Extensive spontaneous subarachnoid hemorrhage over the base of

the brain was most marked about the pons and medulla. Ruptured berry aneurysm of the left vertebral artery measured 4 mms. in diameter. Other findings included congenital hypoplasia of the left kidney, miniature kidney, with small renal artery, ureter patent; compensatory hypertrophy of right kidney; chronic pulmonary tuberculosis.

Other Congenital Defects.—From reports in the literature, the most frequent congenital lesion found in association with congenital cerebral aneurysms has been coarctation of the aorta. Maude Abbott,[1] in 1928, in a series of 200 collected cases of coarctation of the aorta, reported eighteen cases in which death was due to rupture of a congenital cerebral aneurysm. Baker and Sheldon,[2] in 1936, reported similar cases from the literature.

As noted above, in one case in the present series, the adrenal glands were not in their normal position. The main portions of both glands were situated beneath the capsule of the kidneys. We have observed this anomaly with sufficient frequency during routine autopsies to add support to the original theory of Grawitz, who, in 1883, claimed that the so-called hypernephroma, especially those occurring in the upper pole of the kidney, might well be derived from ectopic rests or remnants of adrenal cortex. For this reason we do not favor entire abandonment of the Grawitzian theory for the more dogmatic one which holds that all hypernephromas are renal carcinomas. In spite of perennial argument on this subject in many publications, renal tumors often defy diagnosis and strict pathologic classification.

REFERENCES

1. Abbott, M. E.: Coarctation of the aorta of the adult type. II. A statistical study and historical retrospect of 200 recorded cases, with autopsy, of stenosis or obliteration of the descending arch in subjects above the age of two years. Am. Heart Jour., 3:392, 574, 1928.
2. Baker, T. W., and Sheldon, W. D.: Coarctation of the aorta with intermittent leakage of a congenital cerebral aneurysm: Report of a case. Am. Jour. Med. Sci., 191:626, 1936.
3. Coombs, Carey: Polycystic disease of the kidneys. Quart. Jour. Med., 3:30, 1909-1910.
4. Dunger, K.: Lehre Von den Cystenniere. Beitr. z. Path. Anat. u. z. Alg. Path., 35:445, 1904.
5. Fearnsides, E. G.: Intracranial aneurysms. Brain, 39:224, 1916.
6. Katz, Georg, and Müehe, Erich: Kongenitale Cystennieren mit Hypertonie und Folgezustanden. Zeitschr. f. Urol., 18:453, 1924.
7. McKenna, C. M., and Kampmeier, O. F.: A consideration of the development of polycystic kidney. Jour. Urol., 32:37, (July) 1934.
8. Oertel, Horst: Special Pathological Anatomy. Montreal: Renouf Publishing Co., pp. 324-325, 1938.
9. Sieber, F.: Über Cystennieren bei Erwachsenen. Deutsche Zeitschr. f. Chir., 79:406, 1905.

DISCUSSION

Dr. Leon Herman (Philadelphia, Pa.): I would like to disclaim any important contribution to Dr. Norris' beautiful presentation, except in so far as the value of moral support is concerned. It seems to me that his conclusion, while not stated dogmatically, is based on sound reasoning. I understand it to be a biologic truism that nature does not develop adult structures that are predestined through associated defects to be functionless. There is no question that this kidney has adult glomeruli dissociated from the tubular system. If this is true, that the glomeruli do not develop until the tubular system is complete, then it would seem obvious to me that the defect herein noted was due to secondary degeneration. If that is true, then the cause of polycystic disease, that is the pathogenesis, would seem to have been demonstrated. What the cause is, of course, remains to be determined.

The theory of Kampmeier that polycystic disease is due to the persistence of generations of tubules that under ordinary circumstances disappear, which may in turn cause obstruction of tubules that are destined to become adult, thereby contributing to the polycystic enlargement, finds no proof in this particular study; nor does deficiency in nephrogenic tissues, a theory resurrected by Beson, find any support in the study. I think Dr. Norris has done a grand piece of work and I congratulate him on his presentation.

Dr. Herman L. Kretchmer (Chicago, Ill.): I wish to congratulate Dr. Norris on his splendid presentation and I am grateful for the opportunity to hear him present his point of view on the subject of polycystic kidney.

The presentation of Dr. Martland interested me very much, and I think we are deeply indebted to him for bringing to us the results of his careful, painstaking study. His presentation has a direct clinical bearing on the mechanism of death in a certain number of cases of polycystic disease of the kidneys. I refer to the group that has an associated hypertension and in whom sudden death is ascribed to apoplexy—in the general meaning of the term. That some of them may have another mechanism of death is shown by his demonstration of the presence of these so-called berry

aneurysms of the circle of Willis with resulting subarachnoid hemorrhage.

DR. ROBERT F. NORRIS (Philadelphia, Pa.): I would like to add one thing which I omitted saying. I think it is quite possible that some of the cysts may be former tubules, in accordance with Kampmeier's theory. Those near the pelvis might very easily be persistent generations of tubules, but I don't believe that such a theory can explain the entire picture.

DR. HARRISON S. MARTLAND (Newark, N. J.): In conclusion, I might state that death in adults suffering from polycystic disease of the kidneys is usually the result of uremia.

Many, however, die as the result of cerebral hemorrhage, which is usually an ordinary apoplexy due to the associated hypertension and arteriosclerosis. If these cases were autopsied, a few, thought clinically to be ordinary apoplexies, would undoubtedly prove to be due to congenital aneurysms of the cerebral vessels.

ADENOCARCINOMA OF THE KIDNEY WITH METASTASIS TO THE LUNG

CURED BY NEPHRECTOMY AND LOBECTOMY

J. DELLINGER BARNEY, M.D., and EDWARD D. CHURCHILL, M.D.

From the Surgical Services of the Massachusetts General Hospital, Boston, Massachusetts

Adenocarcinoma of the kidney (hypernephroma) is a neoplasm that on occasion may be treated by removal of the primary growth and an apparently single metastasis. The following case history relates the course of a patient in whom x-ray evidence of a metastatic nodule in the lung was the first sign of disease. A nephrectomy was performed five months later, and fifteen months following the nephrectomy the pulmonary metastasis was excised by sub-total lobectomy. The patient is surviving five years later in good health, without evidence of disease.

CASE HISTORY

E. M., a white, single woman of fifty-five.

The family history was unimportant. Past history irrelevant except that she spent some months in Greece in 1926, during which time, perhaps owing to excessive dust in the air, she developed a cough and lost about 15 pounds in weight.

Examination by our colleague, Dr. Donald S. King, in November, 1931, showed definite dullness at the right apex with increased whispered voice and râles. The left kidney was palpable but was not thought to be enlarged or irregular in outline. The urine showed the slightest possible trace of albumin, but no pus, blood or casts. There was no sputum, nor in fact did it appear at any subsequent time while the patient was under observation.

Roentgenogram of the chest showed moderate enlargement of the heart and great vessels; the aorta appeared more or less tortuous, especially in the ascending portion. "The upper fourth of the right lung shows a definite parenchymal and peribronchial change characteristic of an old tuberculous process. In the center of the left lung, midway between the apex and base, there is a discrete, irregular nodule a little over 1 inch in diameter. If it were at the hilum one would think it was a fibroma; one must suspect a malignant growth in this position. . . ." The radiologist remarked particularly as to the widening of the ascending aorta, and wondered if there was any luetic history (which there was not).

After suggestions from Dr. King that further study, including x-rays and a pelvic examination, would be desirable in an effort to determine the exact state of affairs, the patient decided to go to Baltimore for another opinion.

The report of the examinations in Baltimore showed a blood pressure of 118/80; white blood count 11,500; red blood count 4.88; hemoglobin 70 per cent; slightest possible trace of albumin in the urine; sediment negative; nose, throat and eyes negative; abdominal and pelvic examinations negative. X-ray films showed a "small rounded shadow in the left lung which looks like an old scar." It was remarked that "in the absence of trouble elsewhere and in the absence of any symptoms—this does not mean anything serious." A later report stated that no evidence of malignancy outside of the chest could be found and that although a "clouding of the right apex" was found, no râles were heard. It was later intimated that the shadow seen in the left lung might be a primary growth, but in the "absence of trouble elsewhere—it is extremely unlikely that we are dealing with a neoplasm in the lung." On the whole the attitude of her medical advisers in Baltimore was to adopt a *laissez faire* policy.

Following this examination the patient spent some time in the South, and on one occasion had some gross blood in the urine. She also experienced definite night sweats. Her sisters said she had had these sweats a great many months but had never reported them before. Upon her return from the South she again consulted her physician in Baltimore, who found the enlarged kidney, but told the family he felt the situation was hopeless so far as any interference was concerned, and advised treatment in a tuberculosis sanatorium rather than elsewhere.

Following the sojourn in Baltimore the patient returned to Dr. King on April 11, 1932.

At this time her evening temperature was often found to be 100° or more. She had a moderate sweat every night. No tubercle bacilli were found in the sputum. The urine was acid; no sugar; albumin, slightest possible trace. The sediment showed occasional to few white blood cells per field, with rare to 15 to 20 red cells per field. Blood studies showed a mild hypochromic anemia. Chemical studies were normal.

Abdominal examination showed a large, freely-movable tumor in the left loin, interpreted as an enlarged kidney. The patient looked well nourished and in good condition. In view of the mass in the left loin the patient was referred to J.D.B. on April 14, 1932.

The presence of the large, irregular, non-tender, movable mass in the left loin described by Dr. King was confirmed. This, together with the presence of blood in the urine, suggested a neoplasm of the left kidney. Roentgenograms were taken of the chest and of the kidneys, the report being as follows:

"Examination of Chest: There is soft, mottled dullness at the right

apex as low as the second rib in front. The markings running from this region to the hilus are thickened and beaded, and the hilus glands are definitely increased in size. There is no positive evidence of calcification in the right mid-lung field. There is a larger area of increased density about 2 cm. in diameter in the left lung. This area has a sharply defined margin and the lung markings around it appear normal. In the lateral view it seems to be almost in the mid-lung field.

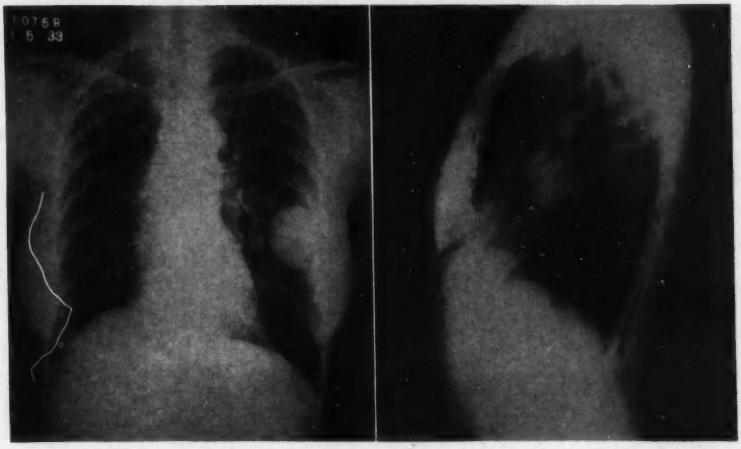


Fig. 1. *(left)* Antero-posterior view of the chest, showing metastatic tumor on the left. This mass is about twice as large as when first observed a year previously.

Fig. 2. *(right)* Lateral view of the chest showing metastatic tumor.

Just in front of it there is a smaller, similar shadow, also a shadow of increased density, near the bifurcation of the trachea, which may be an enlarged gland. The large dull area is in the region of the interlobar septum. The diaphragm is a little high on the right and its respiratory movements are somewhat limited on both sides. The heart shadow is not remarkable. A comparison with the radiographs taken in November is not entirely satisfactory, as the position in which the radiographs were taken is somewhat different, but the dull area in the left lung field appears to have increased considerably in size. The area of mottled dullness at the right apex is about the same in both series.

"Examination of the Genito-Urinary Tract: The outline of the right kidney is distinctly shown; it is normal in size and shape, and is rather low. The liver shadow is a little large. On the left side the kidney outline is not well shown, but there is a dense, somewhat lobu-

lated shadow in this region. The bones of the spine, pelvis and thorax appear normal.

"Conclusions: The appearance at the right apex is that of tuberculosis. The shadow in the lung field is characteristic of a metastatic tumor. A similar appearance could be due to a localized encapsulation between the lobes. The fact that it has increased in size, however, makes this unlikely. The absence of a good outline of the left kidney and suggestion of a mass in this region is characteristic of tumor. The diagnosis should lie between tuberculosis of the lung, pleura and kidney, and hypernephroma of the kidney with metastasis to the left lung with quiescent tuberculosis of the right upper lobe" (Figs. 1 and 2).

In view of the appearance of the left kidney shadow an intravenous pyelogram was done on April 13, 1932.

"Examination of Genito-Urinary Tract—Neo Iopax: Following injection of dye the kidney outlines and pelves are well shown. The right kidney is in normal position and is normal in size and shape; its pelvis is well within normal limits of variation. Usual cupping of minor calices is present. On the left side, the kidney is displaced upward by a large, lobulated mass, the outline of which is fairly well shown and which is apparently connected with the kidney. The lower calices are distorted and the ureter is displaced downward and inward; there is no dilatation of the pelvis.

"Conclusions: The appearance is that of a large tumor arising from the lower pole of the left kidney" (Fig. 3).

As now there was no doubt concerning the presence of a neoplasm in the left kidney, cystoscopic study was considered unnecessary. Before operation the temperature rose to 100 degrees or a little over each evening, definite râles were found at the right apex, and there were moderate sweats every night.

Although the probability was held that the nodule in the left lung was a metastasis from the kidney (x-ray showed a definite increase in size between November, 1931, and April, 1932), operation was thought advisable as no other demonstrable metastases were found. It was thought the mass in the lung might be handled subsequently either by radiation therapy or by operation.

A nephrectomy was done by J. D. B. on April 18, 1932. Gas-oxygen-ether was administered.

Operation Notes: Transverse incision was made on the left, below and parallel to the twelfth rib and extending across the belly of the left rectus. The peritoneum was opened and the intestines retracted with gauze packs. The tumor previously felt was now seen covered with enlarged, tortuous vessels. It was irregular in contour and firm in consistency, obviously a new growth and fortunately freely movable. After dividing the peritoneum and retracting the descending colon toward the median line, a good plane of cleavage was obtained. The kidney was rapidly enucleated until it was attached

only by the pedicle. Three clamps were placed on the vessels and the kidney was removed without difficulty. Ligatures were placed and the clamps were removed without incident. A rubber tissue wick was placed to the pedicle. The peritoneum was closed about the wick, and the abdominal wound was closed in layers.

The pathologic report of the kidney specimen was as follows: "The kidney measures 18 cm. in length. It contains a large, lobu-

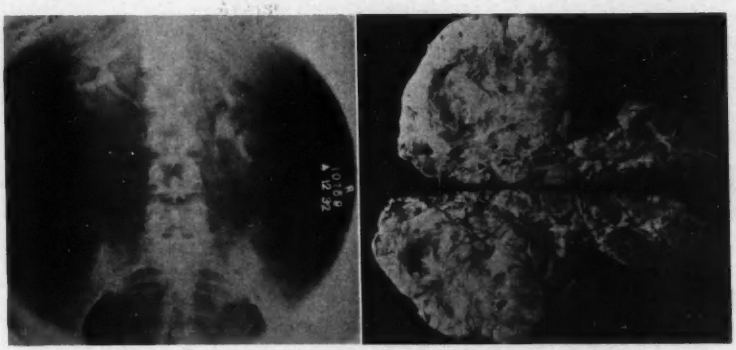


Fig. 3. *(left)* Intravenous pyelogram, showing normal kidney on the right; on the left the pelvis shows a filling defect from the pressure of the large mass in the lower pole of the kidney.

Fig. 4. *(right)* Kidney specimen bifurcated longitudinally shows tumor at the lower pole.

lated tumor mass at one pole, which measures 10 x 7 x 6 cm. The combined weight is 421 gms. On section the tumor shows a soft, pinkish-gray surface in its center, with a yellowish, slightly hemorrhagic periphery. The pelvis is slightly dilated. The capsule strips easily and the renal substance shows nothing noteworthy.

"Microscopic sections show a fairly well differentiated adenocarcinoma composed of large cells uniform in size and appearance, with a few mitotic figures. There are large areas of degeneration. Adenocarcinoma" (Fig. 4).

Convalescence from the operation was uneventful. During it, however, the patient continued to have night sweats, definite râles were found at the right apex, and the evening temperature ranged from 99 degrees to 100 degrees.

Deep x-ray therapy of the nodule in the left lung was started April 28, 1932, ten days after operation. 800 r were given in eleven sittings, in three 10 x 10 fields centered over the lesion in the lung, one anteriorly, one posteriorly, and one laterally. The treatment ended on May 9, 1932, at which time the patient was discharged from the hospital.

From this time until July, 1933, the patient was kept under close observation by Dr. King. No local or general changes in her condition or symptoms were noted during this time, except that the patient eventually gained about 10 pounds. Night sweats continued intermittently, and the evening temperature rose to 99 degrees or 100 degrees at times. Repeated radiographs of the chest showed no changes at the right apex, but in July, 1933, it was noted that the

Fig. 5. Tumor removed from the lung with a portion of the lobe.

nodule in the left lung was about twice as large as it had been in March. During all this long period of observation no subjective or objective signs or symptoms, other than those found by x-ray examination, were caused by the metastatic growth.

The patient was again admitted to the hospital and was seen by Dr. King in consultation with Dr. Frederick T. Lord. Dr. Lord agreed that the nodule in the lung was undoubtedly a metastatic growth and that the patient's outlook without operation was hopeless. Operation was performed by E. D. C. on July 18, 1933, under gas-oxygen-ether differential pressure anesthesia.

Operative Notes: The sixth rib was resected from its angle to the costal cartilage. The pleural cavity was opened and the lung found to be non-adherent. The tumor presented in the lower part of the upper lobe bordering on the interlobar fissure, but not involving it in adhesions. There was no evidence of pleural or lymphatic metastases. Approximately two-fifths of the upper lobe was excised with the tumor. No large bronchi were cut across as the tumor was situated in the lingula. The cut section of lung was repaired by stitch ligatures and the chest closed without drainage.

The pathologic report of the tumor removed from the lung follows:

"Gross: A section of the left upper lobe measuring 14.5 x 6 x 4 cm.

The apex of the lobe is not present. The parietal and interlobar aspects of the visceral pleura are smooth. The specimen contains a large, apparently metastatic tumor mass 6 x 4 x 5 cm. The tumor is firm and completely surrounded by lung tissue except for one area on the medial surface with no lung tissue over it. The cut surface of the tumor is grayish-yellow with several pinkish-yellow necrotic areas scattered throughout. Diagnosis: Metastatic renal adenocarcinoma (Figs. 5 and 6).

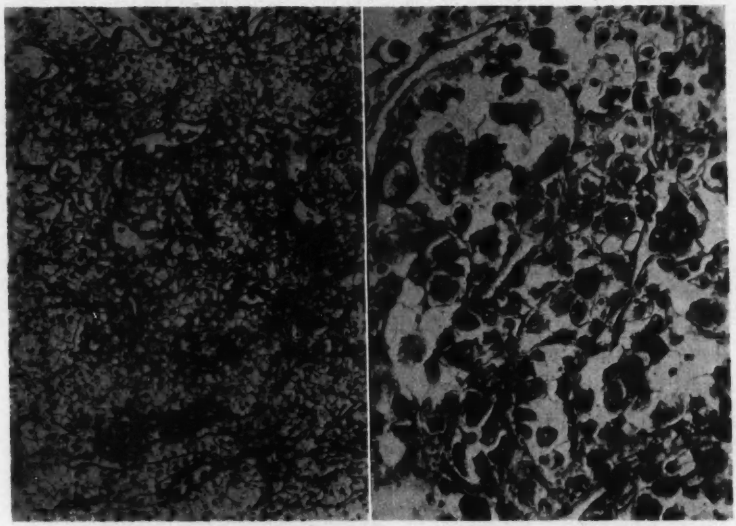


Fig. 6. High dry microphotograph of a kidney tumor on the left and metastatic tumor of the lung on the right. The marked difference in the appearance of tissue is due to more rapid growth of this tumor and also to the effects of x-ray treatment.

"Comment: The tumor cells in this metastasis are swollen, much larger, and more atypical than those seen in the primary renal tumor. This change in appearance may be due to two factors: (1) more rapid growth of the tumor, and (2) the effect of roentgen-ray therapy. There is no doubt, however, that the tumor is a metastasis and not a primary lung neoplasm."

Recovery from this operation was uneventful.

Since leaving the hospital the patient has been seen many times by Dr. King and several x-ray examinations of the chest have been made. Shortly after operation the roentgenograms showed an area of

pneumothorax and a fluid level in the mid-portion of the chest. The heart was not displaced; there was no change in the appearance of the right apex. Subsequent radiographs showed gradual and finally complete disappearance of the pneumothorax and of the fluid. The tuberculous process has shown no evidence of activity and there have been no evidences of the recurrence of the neoplasm. At the present time the patient is in excellent condition; there are no night sweats or other symptoms, appetite good, weight 137½ pounds, temperature normal, blood pressure 110/86. There has been no cough, but râles have persisted above the right clavicle in front and at the right apex in back. Repeated urine examinations have shown an occasional white cell in the sediment, but nothing else.

A careful search of the literature reveals no case identical with the one just reported. It is, however, well known that solitary metastases from kidney tumor may occur, both as an early manifestation of the disease and perhaps as the first and only evidence of it. It is also well known that single or multiple metastases may occur as late as ten years after the recognition and removal of the kidney tumor.

Metastases to the lung occur not infrequently from adenocarcinoma of the kidney. There is clinical and x-ray evidence to show that these may occasionally undergo spontaneous regression. Bumpus[2] reports such a case and Beer[1] mentions two of a similar nature.

When one speaks of a "solitary" metastasis it is meant that only one can be demonstrated. The nature of kidney tumors is such that single metastases are not likely to occur. It is quite probable that others may be present causing no symptoms and undemonstrable, and that in some instances they may undergo spontaneous regression.

As Beer says, "Unfortunately, we do not know just what biologic forces delay the development of these secondary tumors . . . some forces in the patient's body hold them in check for many years, until finally they become clinically evident . . . efforts should be directed toward finding the biologic forces that keep local recurrences and solitary distant metastases in temporary check, as well as the similar forces that cause metastases . . . to disappear completely."

SUMMARY

In the case reported two points are worthy of emphasis:

1. A lung metastasis from adenocarcinonma of the kidney was not radio-sensitive.

2. If a metastasis is apparently solitary and accessible to surgical removal, it is definitely worth while to undertake removal of the metastasis as well as the primary growth.

REFERENCES

1. BEER: Surg., Gynec. and Obst., 65:433-446, (October) 1937.
2. BUMPUS: Jour. Urol., 20:185-191, (August) 1928.

TWO MALIGNANT NEOPLASMS OF URINARY TRACT

(1) BILATERAL AND METASTASIZING RENAL CARCINOMA
(2) SQUAMOUS CELL CARCINOMA OF BLADDER

E. J. McCAGUE, M.D.

Pittsburgh, Pennsylvania

We wish to report this case for the following reasons: (1) Primary bilateral renal carcinomas are extremely rare, there being only twelve authentic cases in the literature. (2) It is the first case of triple malignancy in which primary carcinomas of the kidneys are associated with a squamous-cell carcinoma of the bladder. (3) The unusual clinical manifestations together with a filling defect in one kidney, which, as indicated by pyelography, showed little alteration over a period of eight years.

In reviewing the literature of primary carcinomas in both kidneys, we find only twelve cases. There are reports of many cases of primary bilateral renal tumors of the embryonal type (or Wilms' tumor) which are rarely found above the age of five years, and which are not considered carcinomas. According to Nicolich,[14] the first cases reported in the literature were two by Steffen in 1905 and one by Lubarsch in 1925. In 1926, Chute[4] reviewed a series of forty-three cases of hypernephromas, one of which was bilateral. In the following year, 1927, Verne Hunt[9] added another case. In 1931, Sanford[15] reviewed the literature on multiple primary tumors of the kidney to which he added one of his own which he described as a transitional cell carcinoma arising in each kidney pelvis. This case differs from all the others in this group in that it represents a true pelvic tumor instead of a parenchymatous one. Four years later, in 1935, Springer and Bohrod[16] described two cases of bilateral renal carcinomas. Jeck,[10] in 1926, reported one case of bilateral adenocarcinomas of the kidney. In the same year at the Massachusetts General Hospital, Bauer[2] presented a case of hypernephroma in which Mallory,[2] discussing the autopsy findings, described a hypernephroma in the opposite kidney. In 1937, N. Hortolomei, T. Burghele and M. Streja[8] reported a case of carcinoma of both kidneys. In the same year, Wolf and Donat[18] reported a case of bilateral cystic hypernephroid kidneys.

A case reported by Kinney[12] in 1927 is not included in this number because the diagnosis was based only on clinical and pyelographic studies.

MULTIPLE MALIGNANCIES

A survey of the literature is convincing enough that multiple malignancies are not as rare as they were formerly thought. In 1929, Junghanns,[11] in reviewing a series of 36,408 autopsies, found

Fig. 1. Fig. 2.

Figs. 1 and 2. A comparison of the pyelograms of the right side. There is very little difference between Figure 1, which was taken April 29, 1930, and Figure 2, taken May 25, 1937.

4,912 cases of carcinoma, only nineteen of which were multiple; a percentage of less than one-half of 1 per cent. In the same year Hanlon,[7] in a series of 3,000 consecutive autopsies at the Mayo Clinic, found eighteen cases of double primary carcinomas, only one of which was primary in both kidneys. Warren and Gates,[17] in an extensive review of several series of cases of all types of primary malignancies, found that 1.84 per cent were multiple; but in their own series of 1,078 cases the percentage of multiple malignancies was 3.7 per cent. In this group there was only one case of triple malignancy.

CASE HISTORY

The patient was a vigorous male, aged fifty, complaining of backache, painful and frequent urination of three and one-half years' duration. There was no loss of weight and no symptoms referable to the other systems, nor was there any history of a Neisserian infection. Nothing of note was found on physical examination. The urine was purulent and acid in reaction. External genitalia were normal and the prostate normal in size and consistency. The bladder was in a state of chronic inflammation. There was no retraction of orifices, no ulceration, no obstruction to the catheters, urine from right and left kidneys purulent, no retention in either kidney pelvis. Repeated examinations revealed no acid-fast bacilli. Blood chemistry was normal, phenolsulphonephthalein test, 60 per cent, second hour.

X-ray examination revealed a marked dilatation of the upper portion of the left ureter and kidney pelvis with no definite distinction between them; and irregularity of the shadow in the region of the calices, suggestive of cavitation. The right side was similar to the left, except for some tortuosity and dilatation of the entire ureter. The findings were more suggestive of an acid-fast infection than bilateral cystic kidneys or bilateral renal tumors.

The patient was treated by pelvic and vesical lavage with some improvement in local symptoms. He left the hospital fifteen days after admission, with the following diagnoses:

1. Bilateral renal infection—acid-fast infection suspected but not established.
2. Dilated and tortuous ureters.
3. Chronic cystitis.

Seven years later, in July, 1937, the patient returned to the hospital complaining of hematuria, dysuria, marked loss of weight and strength, and severe upper abdominal distress suggestive of a duodenal ulcer.

Cystoscopic studies revealed the bladder to be in a state of severe chronic inflammation, badly contracted and admitting of but little distention; there were several areas of leukoplakia; urine from right kidney purulent, urine from left purulent and bloody. The carcinoma on the left wall was unrecognized.

Pyelogram of left kidney shows same deformity but little altered as was shown eight years previous.

The clinical course in the hospital was one of progressive decline. There was intense nausea and vomiting, a thrombophlebitis of the veins of both legs, marked elevation in nitrogen retention and extreme emaciation. Death occurred three months after his last admission.

Autopsy Findings.—Both kidneys were larger than normal and

grossly nodular. The ureters were thickened and dilated and the hylic lymph nodes were enlarged and firm. The left side of the wall of the bladder was greatly thickened and indurated as compared to the right.

The left kidney weighed 475 gm. It was larger than the right. The capsule was smooth and unbroken but tightly adherent to a large nodular mass at the upper pole which was distinctly yellow in

Fig. 3. A pyelogram of the left side taken April 24, 1930.

color. The cut surface revealed several rounded and well defined masses of coarse yellow and orange mottled tissue, which had almost completely replaced the normal kidney parenchyma. The largest nodule, located at the upper pole, measured 7 cm. in diameter. It had undergone some cystic degeneration with hemorrhage, thus rendering the tissue soft and friable. A similar but smaller nodule was located at the lower pole. The remaining nodules were located in the deeper parts of the kidney. The walls of the pelvis and ureter were thickened. Tumor tissue had extended into the pelvis, filling the lower portion, as well as the upper end of the ureter.

The right kidney weighed 240 gm. It was similar to the left except that the numerous tumor nodules had not replaced as much kidney parenchyma. Like the left, the largest nodule was at the upper pole; and, likewise, the pelvis and ureter of the kidney were invaded by extension of the tumor growth.

The metastases to distant structures were comparatively small in

number and extent, considering the size of the primary tumors. A small, firm, pea-sized nodule with some smaller nodules around it was present in the pleural surface of the upper lobe of the right lung. Several small pedunclated polyp-like submucosal nodules were present in the small intestines; one, about the size of a marble, was attached to the mucosa of the duodenum by a slender pedicle; and several

Fig. 4. Left kidney. Hypernephroid carcinoma. ×125.

smaller and more sessile nodules were located in the mucosal surface of the jejenum.

The microscopic picture of both primary tumors and the various metastatic growths were identical. The essential tumor cell was a large cylindrical cell of relatively uniform size with clear cytoplasm and a large, round, deeply staining nucleus. The arrangement of the cells was essentially tubular. In the same sections, however, in certain areas the cells tended to be alveolar in arrangement while in others they were in solid masses. In still other areas they were arranged in long cords. The supporting stroma was very scanty, being generally in the form of thin septa between masses of tumor cells. Not all the cells showed a clear cytoplasm. Some were quite granular, with increased cytoplasmic density. Hemorrhage was present in many areas.

The tumor of the bladder involved most of the left wall. The mu-

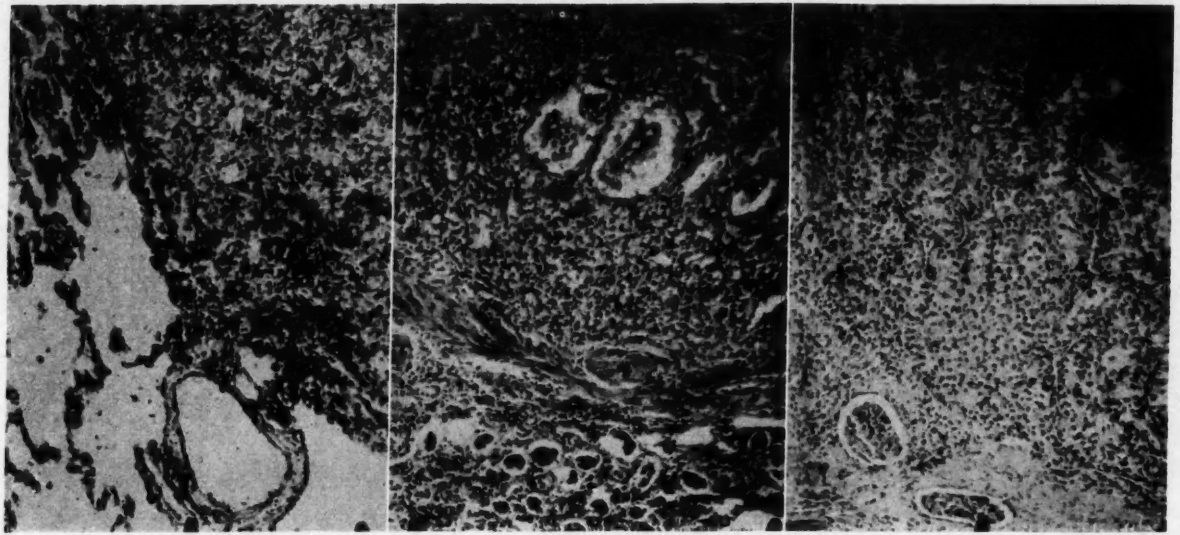


Fig. 5. Right lung. Secondary hypernephroid carcinoma. ×125.

Fig. 6. Jejunum. Secondary hypernephroid carcinoma. ×125.

Fig. 7. Right kidney. Hypernephroid carcinoma. ×125.

cosal surface over the involved areas was ragged and necrotic. The wall itself had been infiltrated throughout its entire thickness, producing a dense, hard tumor with a granular, fibrotic and friable cut surface. The microscopic appearance was that of a squamous-cell carcinoma with cornification. This tumor apparently originated in an area of the mucosa which had undergone metaplasia, since several

Fig. 8. Urinary bladder. Squamous cell carcinoma. ×125.

white, plaque-like areas of leukoplakia were still present in the more normal portions of the mucosa.

The major pathologic diagnoses after autopsy were:

1. Bilateral renal carcinomas of the hypernephroid type with metastases to renal pelves, regional lymph nodes, lung, duodenum and jejunum.
2. Squamous-cell carcinoma of bladder.
3. Leukoplakia of bladder mucosa.

(Richard J. Simon, M.D.)

DISCUSSION

It is difficult to be positive that there is a primary tumor in each side when dealing with symmetrical organs such as the breast,

where there is a fairly direct avenue for transmission of metastases from one side to the other. But with a renal carcinoma, the chief route of metastasis is the blood stream and in the absence of a patent foramen ovale or large pulmonary metastases, it is hard to explain how tumor cells could be transmitted from one side to the other. Retrograde extensions in the veins of other organs have been reported, but very rarely.

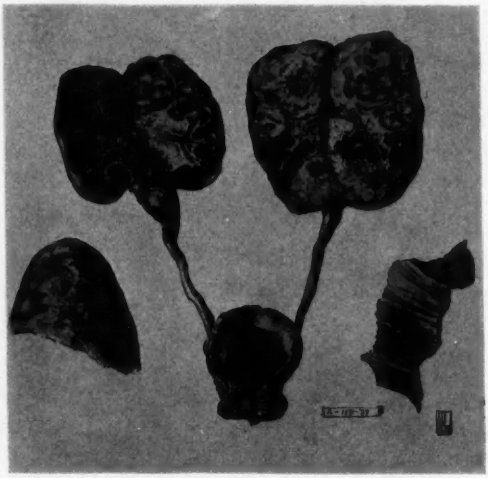


Fig. 9. Bilateral hypernephroid carcinomata of kidneys with secondary tumors in right lung and jejunum and squamous cell carcinoma of urinary bladder.

The kidney has been considered an unusual site for secondary malignancy from any part of the body. Barney and Mintz[1] found forty cases (2.5 per cent) in 1,116 autopsies on patients dying of malignancy and none of these cases had the primary tumor in the opposite kidney. Ferguson,[6] however, reports from the Kidney Tumor Registry that, out of the first fifty cases submitted as primary tumors of the kidney, eight were classified as secondary growths.

In comparing the kidney tumors in this case we find that one is not much larger than the other, and, judging from the pyelo-

grams, there has been very little change in the shadows of the pelves and related structures over a period of eight years. In a secondary tumor the metastases would be expected to be much smaller than the primary tumor, and would tend to be multiple. In forty cases of secondary tumors in the kidney, reported by Barney and Mintz[1] no metastasis was found larger than 3 cm. in diameter and none produced symptoms. With the metastases in the lung and intestine in this case as small as they were, one would be surprised to see a secondary tumor as large as was found in either of the kidneys. The patient gave a history of having pain in both kidney regions for many years and this would indicate that each tumor must have produced symptoms very early.

The microscopic picture of one kidney is identical with that of the other, which is not usual when one is secondary to the other. In a secondary tumor the individual metastases show a constant structure although the type of cell and structure of one might differ markedly from another.

With all these points considered, this case conforms to the criteria postulated by Major[13] and by Warren and Gates[19] to establish the conditions of multiplicity of primary malignant tumors, namely—"Each tumor must present a definite picture of malignancy. Each must be distinct, and the probability of one being a metastasis from the other must be excluded."

The pyelograms of this case indicate relatively slow growth of carcinomas of the hypernephroid type.

If metastases from such tumors progress as slowly, then cases of three- to five-year cures following nephrectomy might be viewed as doubtful and a longer period of time, as a basis of cure, considered.

CONCLUSION

The literature on primary bilateral carcinomas is reviewed and one case added, making a total of thirteen.

The incidence of multiple primary malignancy is reviewed.

The case reported, having also a primary carcinoma of the bladder, is another example of rare triple malignancy.

BIBLIOGRAPHY

1. Barney, J. Dillinger, and Mintz, E. Ross: The occurrence of metastatic malignant disease of the kidney. Jour. Urol., 32:45-51, 1934.

2. Bauer, W., and Mallory, T. B.: Case Records of Massachusetts General Hospital, New England Jour. Med., 214:425-428, 1936.
3. Bell, E. T.: A classification of renal tumors with observations on the frequency of the various types. Jour. Urol., 39:238-243, 1938.
4. Chute, A. L.: A study of cases of hypernephroma. Boston Med. & Surg. Jour., 194:472-478, 1926.
5. Ewing, James: Neoplastic Diseases, 3rd ed. Philadelphia, W. R. Saunders Co., 1928.
6. Ferguson, Russel S.: Symposium on Renal Tumors. Jour. Urol., 39:316.
7. Hanlon, F. R.: Multiple primary carcinomas. Am. Jour. Cancer, 15:2001-2012, (July) 1931, supp.
8. Hortolomei, N., Burghele, T., Strejz, M.: Bilateral tumors of kidney with report of cases of bilateral cancers. Presse med., 45:332-334, (March 3), 1937.
9. Hunt, V. C.: Bilateral hypernephroma. Surg. Clin. N. A., 7:1462-1464, (Dec.) 1927.
10. Jeck, H. S.: Bilateral malignant lesions of upper urinary tract. Jour. Urol., 35:206-212, (Feb.) 1936.
11. Junghanns, H.: Eine Krebsstatistik uber 35 Johre. Ztschr. f. Krebsforsch, 29:623, 1929.
12. Kinney, W. H.: Hypernephroma, with report of case of bilateral hypernephroma. Jour. Urol., 18:533-542, (Nov.) 1927.
13. Major, R.: Multiple primary malignant tumors. Johns Hop. Hosp. Bull., 29:223-231.
14. Nicolich, G.: Ueber beiderseitige Nierengeschwuelste. Ztschr. f. Urol., 23:477-485, 1929.
15. Sanford, H. L.: Carcinoma of both kidneys; report of case with review of literature of multiple primary malignant tumors. Surg., Gyn. & Obst., 53:360-365, 1931.
16. Sprenger, A., and Bohrod, M. G.: Bilateral renal carcinomas. Jour. Urol., 33:427-433, (May) 1935.
17. Warren, S., and Gates, Olive: Multiple primary malignant tumors—a survey of the literature and a statistical study. Am. Jour. Cancer, 16:1358-1414, (Nov.) 1932.
18. Wolff, K., and Donat, R.: Pathologic changes in Lindau's disease: bilateral cystic hypernephroid kidneys; case. Ztschr. f. urol. Chir. u. Gynak., 43:272-292, 1937.
19. Young, H. H., and Davis, D. M.: Young's Practice of Urology. Philadelphia: W. B. Saunders Co., 1926.

THE RELATION OF SO-CALLED ADENOMA OF THE KIDNEY TO CARCINOMA OF THE KIDNEY

HUGH CABOT, M.D., and ANTHONY W. MIDDLETON, M.D.

From the Divisions of Surgery, The Mayo Clinic, and Urology, The Mayo Foundation, Rochester, Minnesota

Much of the recent literature bearing upon renal adenoma and renal carcinoma is devoted to restatement and clarification of theories and observations made by pathologists of the last century and the early part of the present century. We shall here put forward evidence based upon the study of material obtained at The Mayo Clinic and try to draw conclusions therefrom.

METHOD AND MATERIAL FOR STUDY

The material used in this study consisted of: (1) freshly obtained necropsy material which, after fixing in Orth's solution and imbedding in paraffin, was stained with hematoxylin and eosin; and (2) microscopic sections in cases of patients previously subjected to necropsy obtained from the files of the Section on Pathologic Anatomy at The Mayo Clinic.

A total of seventy-six cases was studied. In a certain number, the material could only be examined in the gross state because of technical difficulties involved in obtaining, in sections, adenomas which often were less than 1 mm. in diameter.

The microscopic sections studied consisted of: (1) sixty-one adenomas, of which fifty were of the solid type (forty-seven papillary, two tubular, and one alveolar) and eleven of the type which fell into the rather arbitrarily defined group of papillary cystadenoma; and (2) fifteen cases of typical renal carcinoma in many of which sections were examined from different areas in the gross specimen.

PATHOGENESIS OF ADENOMAS

Two theories stand out as most plausible in explaining the pathogenesis of adenomas: (1) they develop in sclerotic kidneys in association with cysts, and (2) they are associated with abnormalities in the embryologic development of the kidneys.

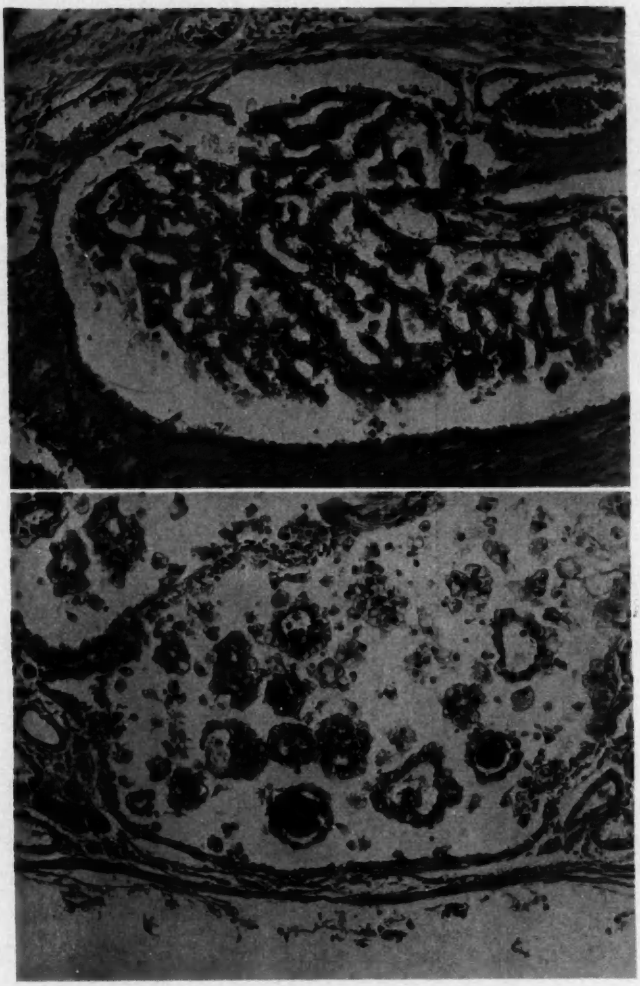


Fig. 1. Renal adenoma, showing evidence of secondary cyst formation.

Fig. 2. Renal adenoma of the papillary type.

1. In support of the first theory, it may be said that the coexistence of renal adenoma and multiple subcapsular cysts in the scarred arteriosclerotic kidney has long been known. In Nuernberg's series of sixty-six cases of adenoma, either gross or microscopic cysts were associated in 97 per cent. It is not clear whether the cyst is an antecedent or a sequela of the adenoma. Both views are tenable. In some instances of cystic adenoma, the evidence of regression is unmistakable. The cellular structure, the presence of a fibrous capsule, and the presence of deposits of calcium all indicate a process of considerable duration. The cysts in these cases are obviously the result of degeneration rather than the forerunner of adenoma (Fig. 1). In the case of other cysts, serial sections occasionally show them to have an irregular, dilated, and tortuous configuration suggesting their origin from normal tubules. The work of Oliver and Luey on renal architecture has shown that the tubule of a hyaline glomerulus does not always collapse and atrophy but may hypertrophy and give evidence of fluid retained within the lumen. It is conceivable that repeated infolding and proliferation of the tubular epithelium could produce the papillary form of adenoma (Fig. 2).

The link between cyst and adenoma appears to be complete in the papillary cystadenoma which partakes of the elements of both structures. Papillary projections into cyst cavities are seen in all stages of development. As early as 1882, Sabourin regarded the proliferating papillary projections as representing a transition from cyst to adenoma. As the epithelial buds arise in the cyst wall, they push forward into the cavity and, by repeated subdivision, form a series of branch-like projections in which central connective tissue trabeculæ support the epithelium. The cytoplasm of the epithelial cell is granular and may be either dark or light.

The frequent appearance of adenomas in connection with the multiple cysts of the arteriosclerotic kidney suggests that other renal cysts may give rise to adenomas. It is not impossible that the polycystic kidney may prove an interesting field for the study of the development of adenomas. That adenoma may develop in a polycystic kidney is attested by one example included in this series. The typical adenomatous structure, apparent in such intimate relation with the cystic elements, leads inevitably to the conclusion that their coexistence is not accidental.

2. The other commonly accepted theory of the origin of adenomas is that they represent an aberration from the normal development of the kidney. As in the case of displaced adrenal tissue, perhaps only a small percentage of abnormally placed renal tissue undergoes neoplastic transformation. Albarran, in 1897, described misplacement and imperfect development of renal tubules in the capsule and cortex of the embryonic kidney and suggested that renal neoplasms could here originate. Ewing has suggested that the same miscarriage of embryonic development of the uriniferous tubule which produces congenital cystic kidney may be the initiating factor in the development of cystadenoma. Stoerk suggests that the alveolar type of adenoma may develop from preexisting convoluted tubules.

GENERAL CHARACTERISTICS OF RENAL ADENOMAS

Frequency.—The incidence of renal adenoma is higher than is usually realized. Nuernberg found sixty-six examples in 2,250 necropsies. Dunn's intensive examination, for aberrant epithelial structures in eighty consecutive necropsies, revealed adenomatous tissue in 11 per cent. In Weichselbaum's series, there were no examples of adenoma in individuals under thirty years of age. In individuals above that age, the incidence gradually increased, becoming 10 per cent in subjects over eighty years old. In our study, the increasing prevalence of adenoma, in the decades past middle life, is striking. As has frequently been pointed out, this increase is significant because it parallels the incidence of vascular disease of the kidney.

Gross Appearance.—Adenomas appear grossly as single or multiple grayish white or yellowish nodules usually located in the cortex of the kidney. Small adenomas may resemble military tubercles. Larger ones have a slightly yellowish color with occasional areas of mottling. Most adenomas occur singly without predilection for either kidney. They frequently occur in both kidneys. In gross appearance there is no way in which adenomas may be definitely differentiated from adrenal rests or leiomyomas.

Microscopic Appearance.—In their microscopic appearance, three groups of renal adenomas have been described: papillary, alveolar, and tubular. The papillary variety includes most of the adenomas.

Microscopically they consist of cystic spaces into which project numerous papillary processes. These processes may be seen in varying degrees of proliferation, from a few strands with almost no branching to very luxurious ramifications which completely fill the cystic cavities. The connective tissue trabeculæ are covered by a layer of cuboidal or cylindrical epithelium whose cells may be small, granular, and opaque, or large and clear with granules of doubly refracting lipoids (Fig. 2).

The alveolar type of adenoma is characterized by polyhedral cells arranged in alveolar fashion. Many alveolar spaces are of the size of convoluted tubules and are completely filled with these large cells (Fig. 3).

The tubular adenoma is rare. It consists of long irregular canals lined by small fat-free cells with large nuclei. Only one example of tubular adenoma appeared in the specimens examined in this study.

RENAL CARCINOMAS

The most commonly used classification of renal carcinomas divides them into two main groups: the papillary and the alveolar. Typical clinical courses have been ascribed to each type. However, the ultimate differentiation as to type depends entirely upon microscopic appearance and not upon gross appearance or clinical behavior. Very early in the study of renal adenomas the theory was put forward that there was a transformation from the benign to the malignant type, with the cell type staying true to form; that papillary adenocarcinomas developed directly from papillary adenomas and that alveolar adenomas beget alveolar adenocarcinomas. The suggestion of transformation from adenoma to carcinoma is most striking in the papillary form.

Papillary Adenocarcinoma.—The most common variety of renal carcinoma is the papillary type with clear cells. This was the type to which Grawitz gave the misleading name "hypernephroma" and for that reason since that time it has been difficult to determine the incidence of this type until within relatively recent years. The renal origin of this tumor is now generally accepted. These growths appear first under the capsule of the kidney, which is distended to allow the tumor's expansion. The characteristic color is yellow to orange. Necrosis and hemorrhage are frequent when the growth becomes large. Small cysts containing gelatinous or

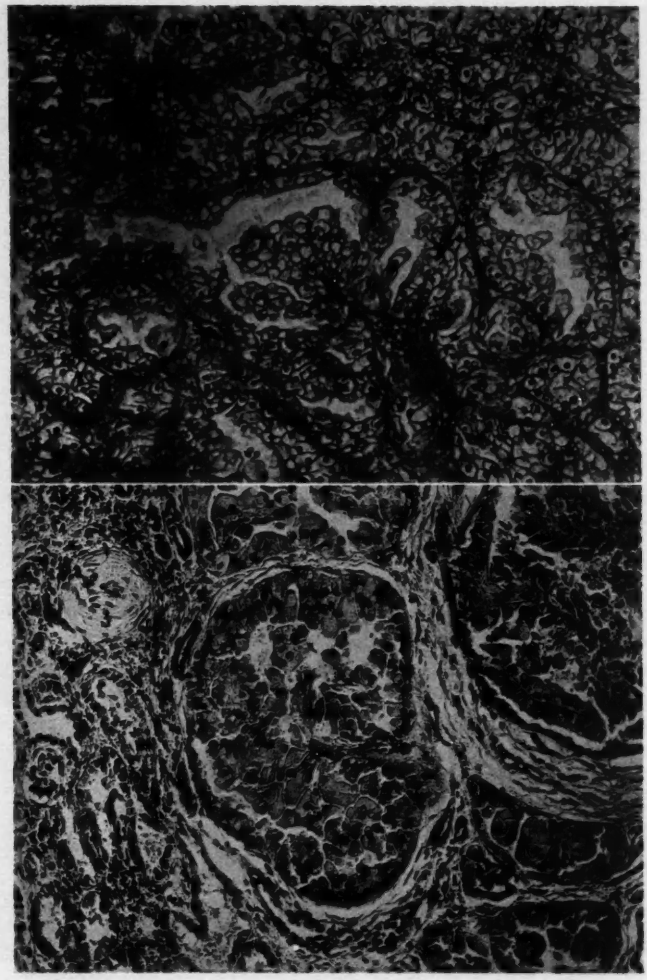


Fig. 3. Renal adenoma of the alveolar type.

Fig. 4. Renal carcinoma of the papillary type, with clear cells.

brownish material are frequently seen. By their coalescence, large cystic cavities may develop. There is usually no capsule, but the tumor remains fairly well circumscribed in the early stage of its development. Microscopically, the distinguishing feature is the clear glassy cells which are arranged about trabeculæ in a variety of different patterns, ranging from a single layer of high cubical or cylindrical cells to more complex patterns in which the cells are large and appear heaped up to the depth of several layers (Fig. 4).

Alveolar Adenocarcinoma.—The other main type of renal carcinoma is the alveolar adenocarcinoma. These tumors constitute only a small portion of malignant renal tumors in adults, yet they are as a rule so highly characteristic as to warrant recognition and study as a separate group.

A number of hypotheses have appeared in attempts to explain the origin and development of these tumors. It is generally agreed that they have a renal origin. The microscopic structure usually includes cell patterns strongly suggesting the appearance of renal tubules. Whether these tumors' lineage is through preformed tubules or more embryonal structures cannot be definitely stated. They may occur in either the infant or the adult. The adult tumor includes most alveolar adenocarcinomas, and its structure may be considered typical of the group. These tumors may arise from any portion of the kidney, or may even have an extrarenal origin. Grossly they have a solid, lobulated, opaque structure, and tend to remain circumscribed in the early phases. In later stages, especially in the more malignant forms, they metastasize extensively through the veins and the lymphatics. Cysts containing gelatinous material often appear. The resultant appearance has been called a "colloid carcinoma." Microscopically some segments of renal tubules are usually simulated.

The foregoing description of the various forms of renal carcinoma is almost universally adopted, and is, on the whole, quite satisfactory. Most of these tumors fall quite definitely into set categories. However, this classification, like others in general pathology, has the defect that some classes and divisions are more descriptive of the appearance of the structure than of the pathologic processes involved. It is not unknown for a single tumor to show quite diversified histologic pictures within adjacent areas. At least

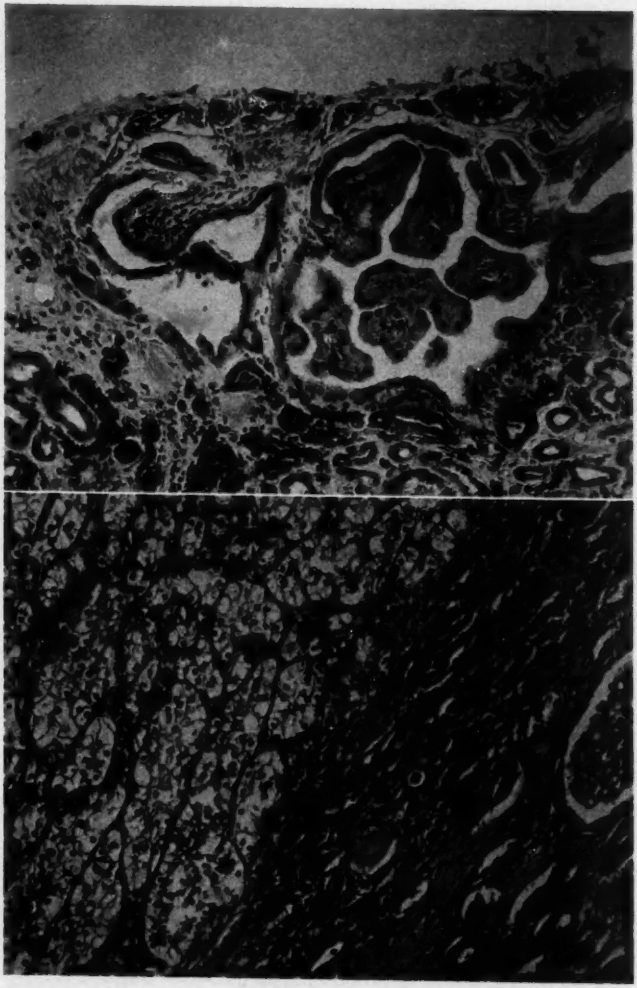


Fig. 5. Renal carcinoma of the alveolar type, with both clear and dark cells.

Fig. 6. Renal adenoma with regular cells.

one example in this study showed typical dark cells and clear cells both in the same section (Fig. 5). This finding at least suggests a common origin, and probably common or very closely related modes of development of all renal carcinomas.

RELATION OF RENAL ADENOMAS TO RENAL CARCINOMAS

What is the relation, if any, between these carcinomas and adenomas? As the historical survey indicated, their epithelial origin has been long recognized. Sturm's contention (1875) that adenomas undergo a slow transformation into carcinomas was supported by Stoerk, Zehbe, Nobiling, and others within the following decade, and by many investigators since that time. The corollary to this statement is, of course, that these tumors are of essentially different nature, the carcinoma being of undisputed malignancy, and the adenoma showing no evidence of those aberrations from normal structure which denote malignancy.

An intensive examination of the material available for this study has led to the conclusion that no hard and fast rule can be drawn between the alleged benignancy of the adenoma and the asserted malignancy of the carcinoma. The histologic features which stamp the carcinoma as an unquestionably malignant tumor are found in the adenoma to a less recognizable degree. This assertion in no manner denies to Sturm and his followers the possibility that tumors with adenomatous structure may become full-blown carcinomas with unquestionable invasive qualities. Indeed several examples of such apparent transition were seen in this study. The emphasis here is laid rather on establishing a new sequence of events.

We suggest that the same forces which initiate the formation of the adenoma may also initiate the formation of carcinoma. This conclusion is based on the following points:

1. Age incidence.
2. The coincidence of carcinoma and adenoma in the same kidney.
3. Lack of uniformity in the structure of adenomas.
4. The cellular structure of adenomas.
5. The evidence of all degrees of malignancy as traced in a succession of microscopic sections.

1. *Age Incidence.*—The age incidence of renal adenoma has already been discussed, with particular attention called to the fact that this lesion occurs as a rule in late middle life, the prevalence increasing with each successive decade.

As in other organs, carcinoma of the kidney is essentially a disease of man's later years. Although it is occasionally seen before middle life, its full ravages do not appear until the accumulation of degenerative forces or the release of inhibitory forces within the tissue permits the neoplastic cells to overrun the normal cells. The average age of patients with carcinoma in the present study was sixty-one years. By comparison, the average age of patients in whom adenomas were found was fifty-nine years. In Trinkle's study of adenomas, the average age was sixty-two years. Other studies have produced comparable figures. Sufficient data are available to permit the conclusion that adenomas and carcinomas occur at approximately the same age. This fact should arouse more than passing interest.

Abundant clinical and pathologic observations lead us to conclude, or at least to infer, that neoplasia is an ever-present menace to the existence of every individual. By middle life, in the usual instance, the soil is prepared for this menace to become an actuality. Abnormal neoplastic cells then appear in a number of bizarre patterns, growing with varying degrees of destruction to the normal tissues. The one common factor in all these tumors, from the most benign to the most malignant, is their origin. Despite their potential danger, all are equally harmless before the release of the assumed inherent property by which tissues strictly limit their own extension. The release from this limiting control probably occurs near the same time for all degrees of malignancy within the same class of tumors, regardless of how destructive the ensuing process may be.

There is no better specific example of this general statement than the foregoing facts about renal adenomas and carcinomas. The close parallel between the ages of greatest incidence of the two tumors is a direct refutation of two contentions: (1) The benignancy of adenomas; as a rule tumors which are considered strictly benign do not first appear within a group of years so sharply limited as do the renal adenomas, and the recognition of benign tumors is not restricted to the years of senescence, but they

may occur over a period of several decades, most usually much earlier in life; (2) the frequent transformation of so-called benign adenomas into frankly malignant carcinomas. Renal adenomas are relatively slow-growing. If carcinomas developed from these adenomas, the age incidences would not be so nearly the same as they actually are. Instead the adenoma should antedate the carcinoma by an interval varying from a few to many years.

2. *Coincidence of renal carcinoma and adenoma.*—Occasionally a kidney examined grossly presents both a carcinoma and single or multiple adenomas. Several such examples were seen in this study. This combination of tumors in one specimen, although not frequent, is common enough to be beyond the possibility of mere accident, and quite common enough to merit speculation about a possible relation between the two lesions.

Obviously the fact of proximity alone does not determine the similarity of structure of tumors within the same organ, but this fact assumes importance when it is so frequently linked with other findings: the tendency of these multiple adenomas to have about the same degree of histologic developement, and notably their tendency to appear at approximately the same age as unquestioned cancer. The situation actually represents the culmination in widespread areas and at approximately the same time of the pathologic changes, as already described, which result in the formation of adenomas.

Multiple renal adenomas may be compared with tumors which in another location show a marked tendency to multiplicity and similarity of structure, namely, in the urinary bladder. Until fairly recently these bladder tumors were considered benign, but continued clinical observation has proved them to be malignant.

3. *Lack of uniformity in structure of adenomas included in the same group.*—The three classes of adenoma have been described. Within each class the cellular structure usually reproduces quite faithfully the type pattern, but critical examination of large numbers of adenomas reveals that this invariability of structure is more apparent than real. A few examples may illustrate some of these variations:

One gross specimen contained two adenomas situated a few

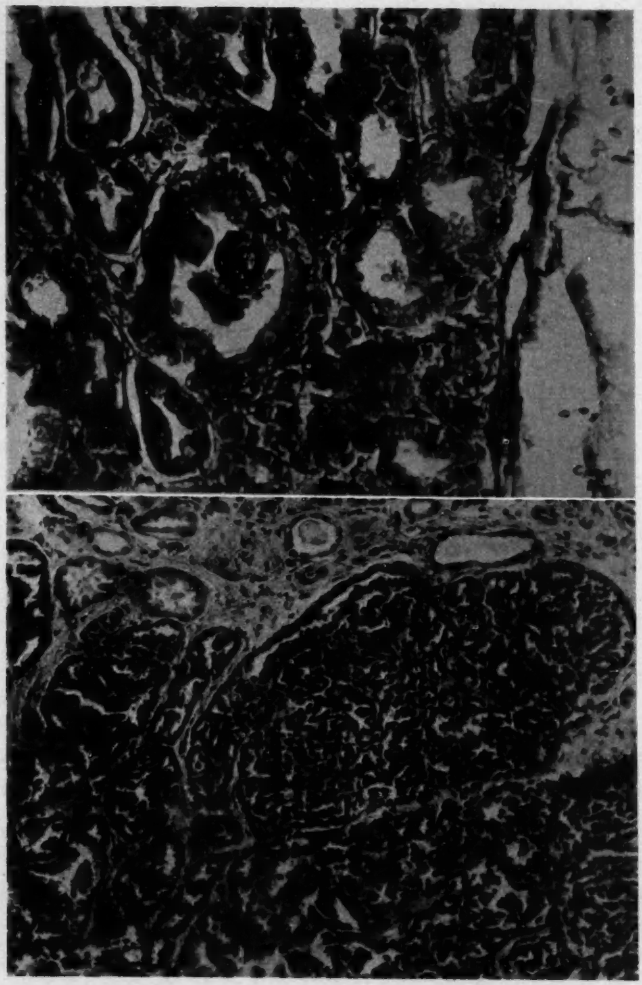


Fig. 7. Adenoma, in same kidney as in Figure 6, with irregular cells.

Fig. 8. Small renal carcinoma.

millimeters apart. In the gross state their appearance was identical. By careful preparation, both were included in the same microscopic section. Despite the presumptive evidence of the similarity in their origins, their histologic appearance showed the greatest possible divergence. In the smaller adenoma (Fig. 6) a series of irregularly dilated cystic spaces appear, lined with a layer of singularly uniform cells. These cells were united in layers as regular as those forming the tubules in normal renal tissue. In fact the resemblance between these cells and normal renal cells was quite apparent in most respects except for the cystic configuration of cell groups, and a very slight difference in the staining reaction with hematoxylin and eosin.

The larger adenoma (Fig. 7) retained some of the same general characteristics and yet was radically different. The cells were no longer so nearly regular, but varied considerably, both in size and outline. They tended to be more deeply stained, more densely packed, and had a less regular pattern.

These two papillary adenomas may be considered to be at opposite poles in the variability of cell pattern. All examples approach in their main characteristics either one or the other, yet careful examination in many instances reveals varying degrees of difference from both of these types.

The following conclusion may rationally be drawn from these observations: Adenomas are derived from renal elements whose structure is invariable. Accepting adherence to a known cellular pattern as the criterion of normal, or nonmalignant, tissue, the occurrence in varying degrees of deviation from this pattern suggests a malignant nature for adenomas.

4. *The cellular structure of adenomas.*—With due allowance for the strength of the foregoing points in support of the present thesis, the burden of proof of the malignant nature of renal adenomas must be borne by the evidence contained in the microscopic appearance of the cells composing these tumors. Neoplasia, when reduced to its fundamental meaning, is a transformation, not of tissues, but of individual cells. The fact that clinical manifestations of tumor formation depend on the mass action of tumor tissue exerting its influence on vital structures does not detract from the truth of this statement.

The problem of the status of renal adenoma resolves itself into a question of comparisons. How nearly does the individual cell in the adenoma approach the structure of the normal renal cells which surround it?

The cells seen in renal adenomas represent not only a deviation from normal renal cells, but a deviation in the direction of distinct malignant characteristics. As a general rule, the nuclei take a deeper stain than in normal renal cells; they may be irregular; and they are often increased in size, both actually, and in relation to the cytoplasm.

Not every example of adenoma presents all of these characteristics, nor are they at all times so clearly delineated as to be unmistakable, as in a high-grade carcinoma. Study of a number of examples reveals such combinations of these characteristics as might suggest the erroneous conclusion that the deviation from normal is in the direction of malignancy.

An extensive study of any considerable number of adenomas, however, prevents adherence to any such belief. Occasional tumors of microscopic proportions have characteristics which, by all standards of pathologic histology, can be nothing but malignant.

One excellent illustration is reproduced here (Fig. 8). In its greatest dimensions (verified by taking additional microscopic sections in adjacent parts of the same block of tissue), this tumor hardly exceeds the breadth of a normal glomerulus, yet it appears no less malignant than a frank carcinoma many times its size. Its structure is not typical of that usually seen in adenomas, being neither cystic nor papillary in character. It is unnecessary to apply any theory of benign-to-malignant transformation or to envisage extensive growth and tissue invasion to strengthen the contention that this is a malignant tumor. The individual cells represent such a digression from the normal renal cells that their malignant nature can hardly be questioned.

Arising as it does, this type of tumor is obviously no transitional stage between benign and malignant growths. Both size and form stamp it as a malignant growth from its very beginning.

5. *Evidence of all degrees of malignancy as traced in a succession of microscopic sections.*—Systematic search through large numbers of sections of renal adenomas and carcinomas reveals many degrees of deviation from normal renal tissue. These may

be arranged to form a succession from adenomas whose structure quite closely approximates that of normal, completely differentiated tissue, to growths whose carcinomatous nature nobody can deny. This succession inevitably presents overlappings, but there are no points where it is broken.

CONCLUSIONS

1. Renal adenomas occur most frequently in the years of greatest incidence of degenerative vascular diseases. There is no conclusive evidence to contest the repeated assertion that adenomas are usually formed as a result of occlusion and dilatation of renal tubules.

2. The cystic spaces commonly found in papillary adenomas probably represent, in most cases, the stage of development preceding the formation of the multiple papillary projections that compose this tumor. However, the presence of calcium and other evidences of chronicity in some examples suggest that cysts may also occur as a result of degeneration of an adenoma. One microscopic section suggests that adenomas may occur in association with polycystic disease.

3. The renal adenoma is not a transition stage between tissue of benign character and tumors of known malignancy, as is commonly stated, but is of itself a malignant growth. The reasons for this assertion are presented.

REFERENCES

1. EWING, JAMES: Neoplastic diseases. Ed. 3. Philadelphia: W. B. Saunders Co., 1928, pp. 782-796.
2. OLIVER, JEAN, and LUEY, ANN S.: Plastic studies in abnormal renal architecture. II. The morphology of the abnormal nephron in terminal hemorrhagic Bright's disease. Arch. Path., 18:777-816, (Dec.) 1934.
3. TRINKLE, A. J.: The origin and development of renal adenomas and their relation to carcinoma of the renal cortex (hypernephroma). Am. Jour. Cancer, 27:676-689, (Aug.) 1936.

DISCUSSION

DR. LEON HERMAN (Philadelphia, Pa.): Dr. Barney's discussion of the clinical history of the patient with symptoms of low-grade sepsis due to renal tumor interests me because of an experience we have recently had. Of course, since Israel first described fever as a symptom of malignancy of the kidney everyone has been familiar with it. But it rarely pursues the course as in the case which I am about to report.

This patient, a man aged forty-five, presented the general picture of low-grade sepsis three years ago; there was fever at night, and severe sweating associated at times with chilly sensations. There were no urinary symptoms until very recently. He was thoroughly studied in several institutions, and about a year ago was brought to Philadelphia, where the condition was again thoroughly investigated without diagnostic results. At this time he was obviously weak and very anemic, his hemoglobin being 60. Having found a few red blood cells in the urine he was subjected to a complete urologic study which disclosed a pyelographic defect on the left side characterized by excavation in the lower pole of the kidney. This pyelogram lacked the usual characteristics of neoplasm. Radiograph of the lungs disclosed a few minor feathery nodules. His blood cultures were sterile, but it was our opinion, concurred in by various consultants, that this patient had a carbuncle of the left kidney with metastatic lesions in the lungs. The involved kidney was exposed and removed together with the thickened edematous fat en masse. I thought we were removing a carbuncle-bearing kidney, but incision of the mass disclosed a necrotic hypernephroma. In this instance, the entire clinical picture over a period of three years was that of low-grade sepsis.

I would also like to report a case of bilateral papillary carcinoma of the kidney in connection with Dr. McCague's case. This patient also had papillary tumors of the bladder. It was our opinion at the time that the right kidney alone was involved, and accordingly a right uretero-nephrectomy was performed. Later an attempt was made to remove the bladder tumors by fulguration. However, it was soon discovered that the patient had a tumor of the opposite kidney.

DR. WILLIAM F. BRAASCH (Rochester, Minn.): The degree of malignancy in a renal neoplasm is a relative term. The cellular morphology might indicate a variable degree of malignancy, while the clinical course can be that of a benign tumor.

Our pathologist, Dr. Robertson, has often demonstrated the occurrence of renal adenomata such as Drs. Middleton and Cabot described, and he has shown that they often assume a malignant morphology. I have wondered why clinical evidence of renal malignancy is not observed more frequently, since renal adenomata are so common. As a corollary it may well be asked, what is the factor which prevents active extension and clinical manifestation of malignancy in these frankly malignant tumors?

The same question may be raised in the case reported by Dr. Barney. That pulmonary metastasis with renal carcinoma should usually be regarded as contraindicating nephrectomy is indicated by a series of cases of renal tumor operated on at the Mayo Clinic which I reported several years ago. Included in this report were six cases that had roentgenographic evidence of pulmonary metastasis. The kidney was removed and all patients were reported dead, within two years following operation. It is, therefore, open to question in our minds whether in the presence of pulmonary metastasis nephrectomy is indicated. It is conceivable, however, when a pulmonary metastasis has remained stationary for a long time and is confined to a comparatively limited area, as in the case reported by Dr. Barney, that nephrectomy may be permissible with subsequent removal of the metastatic area. It is my impression, however, that such cases are exceedingly rare and in most cases with roentgenographic evidence of pulmonary metastasis surgery is definitely contraindicated.

The diagnosis of pulmonary metastasis may be very difficult. I have repeatedly seen roentgenologists differ widely in the interpretation of pulmonary shadows. In such cases the patient should be given the benefit of the doubt by advising nephrectomy.

I would also say, in regard to Dr. McCague's interesting report, that it is curious that bilateral hypernephroma is not observed more frequently, in view of the frequent bilateral occurrence of renal adenoma.

DR. HERMAN L. KRETSCHMER (Chicago, Ill.): The question of operating upon a patient in whom a diagnosis of metastatic carcinoma of the lung has been made, presents several interesting problems. In the first place, it may be very difficult at times to state definitely that the changes seen in the roentgen film are really due to the presence of metastatic carcinoma. If, for example, the shadow in the lung is not due to carcinoma, but is incorrectly diagnosed as such, it may deprive the patient of his chance to get well, *i.e.*, a surgical removal of the primary focus.

In the second place, while it is true that most of the patients with

lung metastases die relatively soon after the diagnosis has been made, there are some exceptions to the rule and under certain circumstances operation may be advised in spite of the presence of lung metastasis.

Bearing directly upon this point, I would like to mention the case of a doctor upon whom I made a pre-operative diagnosis of hypernephroma. A routine roentgen-ray examination of his chest was made. Two competent roentgenologists diagnosed metastatic carcinoma of the lung. A nephrectomy was done and the diagnosis of hypernephroma was verified. The operation was followed by roentgen therapy of both lung and operative wound. The doctor is still living and well and practicing medicine in the country, seven years afterwards.

I realize, of course, that a case of this kind is open to criticism to the effect that the two roentgenologists may have been wrong. On the other hand, to have accepted their diagnosis and not to have operated upon the patient would at least in this case have been wrong in the light of subsequent events.

As Dr. Braasch has said, it is very difficult at times to correctly interpret shadows seen in the lungs that are attributed to malignant disease.

Therefore, a great deal of thought and consideration must be given to each case so as not to deprive the patient of his opportunity to get well.

The presence of a metastatic lesion in the lung did not stop Dr. Barney from doing just that. Dr. Barney not only did a nephrectomy, but had Dr. Churchill do a lobectomy, and I wish to congratulate him on his splendid result.

DR. EDWIN DAVIS (Omaha, Neb.): In connection with Dr. McCague's presentation, I wish to mention very briefly a case of multiple malignancy of the urinary tract. The individual was a young man in the forties who has just died. He showed advanced carcinoma of the prostate as well as multiple carcinomatous nodules involving the pendulous portions of both the corpora cavernosa and the corpus spongiosum. I mention this because no case has come to my attention of metastasis or direct extension of a malignant growth from the cavernous body to the prostate or vice versa.

DR. HUGH CABOT (Rochester, Minn.): I do not think I have anything to add to what I said. I should like to get on the record, though, a case of bilateral renal tumor which occurred many years ago on the service of my brother, Dr. Richard Cabot, who was going over the autopsy cases. It was long before the days of modern urological diagnosis. It concerned a man with bilateral tumor with evidence of malignant disease though without hematuria and, in discussing the probabilities, I said that this almost certainly was not a renal neoplasm because it was too bilateral. The pathologist let me

down. It was a typical case of what we now call carcinoma of the kidney.

Dr. J. D. Barney (Boston, Mass.): I appreciate the discussion which these gentlemen have made of this case. I agree with the idea that in the first place the patient should be given every chance of having what appears to be a single metastasis, especially if it is successfully, as it was in my case, operated upon. Of course, it does not happen always that the patient has so easily accessible a metastasis. This patient did. One can conceive of metastatic tumor of the lung which would be beyond surgical relief, even with our modern chest surgery.

It is also, as Dr. Kretschmer and others have pointed out, very easy to mistake shadows in the radiographs of the lung for metastases when they are really not. For instance, I had a case about four and one-half years ago of what we called, for lack of a better term, extrarenal hypernephroma, which I am planning to report, a hypernephroma which was attached by adhesions to the lower pole of the kidney, infiltrating the peritoneum and producing a great deal of adhesion between the omentum, intestine, peritoneum and so on. This was excised, leaving a perfectly normal kidney behind, and the man has now, four and one-half years later, a perfectly normal kidney and is normal in every respect. He came into the hospital in another city this winter with a history of "hawking," as he expressed it, hawking up some blood, but no other symptoms referable to his chest. They had radiographs taken showing two masses in his chest, small in size, perhaps as big as a dime. They said he had metastatic hypernephroma. They gave him deep x-ray therapy. As it was done in a place where I do not believe the x-ray machine was very powerful, I don't think the x-ray therapy amounted to much. At any rate, he brought the plates to us and we had some more x-rays and there were no shadows seen in the lung. It may be that the x-ray did, after all, clear up these metastases, but our x-ray man, Dr. Hampton, thought instead of being metastases in the lung, they were infarcts and pointed out from other cases that infarcts of the lung may not infrequently arise and may be mistaken for metastatic tumor and may, by the same token, disappear, which seems to be the case here.

I would like to ask Dr. Kretschmer what the nature of the kidney tumor was to which he refers.

Dr. Bumpus reported a case, I think, of hypernephroma with lung metastases where the metastatic tumor had disappeared in a most spectacular manner, apparently spontaneously.

I think that is about the story, but it seems to me that we should give these patients a chance by taking out the kidney and the single metastasis, if it can be done.

SECOND DAY, MAY 3, 1938

ADRENAL CORTICAL SYNDROMES AND ADRENAL TUMORS

GEORGE F. CAHILL, M.D.

From the J. Bentley Squier Urological Clinic, Presbyterian Hospital, New York City

The adrenal cortex has long been known to be essential to life. Destruction of the adrenals by disease, as a cause of death, was described by Addison; later, Brown-Sequard found that fatal results followed the experimental removal of both glands in a number of laboratory animals. The part of the adrenal necessary for life has been shown by many experimenters to be unquestionably the cortex. It was for disease in the form of tumors of the cortex to project symptoms into a clinical picture that suggested other functions of the cortex besides life maintenace. The earliest recognition of one of these functions was the description of masculinizing changes in females associated with adrenal tumors. When such tumors occurred in female children, maturity was also seen to occur with the masculinization. It was also observed that in male children male adult maturity was the result and there were described, as well, alterations in the metabolism of the skin, subcutaneous tissue and other parts, and in addition in the emotions. With the masculinization tendencies of the female there was associated a depression of the female characteristics. Later it was shown that more rarely the reverse occurs, a feminization of some males with cortical tumors (Holl,[19] Lisser,[22] Simpson and Joll[36]). From observations upon cortical tumors there have been assembled a multitude of changes in the individual that clinically suggest that there may be many functions directly or indirectly determined by the adrenal cortex. However, it has been shown that somewhat similar symptoms are seen when tumors are present in other hormonal glands, as the pituitary, pineal, thymus, ovary and testicle, and the interpretation of the part played by each gland in the picture is somewhat confused. In addition, as far as the more frequent symptoms that are seen when adrenal cortical tumors are concerned, investigation has shown that simi-

lar or closely resembling syndromes appear much more frequently without any demonstrable tumor and a hyperfunction of the adrenal cortex has been assumed to play a part in their production (Broster and Vines,[4] Cahill[8]).

It has been only recently that experimental work by various investigators supports the clinical observation that the cortex of the gland may occupy a position in the endocrine system second

Fig. 1 *(left)*. G. C., a female, aged sixteen, with androtropic tumor. The photograph shows a few days' beard growth and acne of the skin. This beard growth persisted after removal of the tumor, although the other masculine traits abated rapidly and her femininity completely returned.

Fig. 2 *(right)*. Same case. Radiograph of 24-hour air injection of adrenal. The globular tumor mass is seen with a projection up into the space between the spleen and the spine. Below the tumor, the outline of the kidney may be dimly made out.

only in importance to the pituitary. Comparatively early from the medulla came the discovery and later isolation of epinephrine, the first hormone to be crystallized, identified, and synthesized. With apparently much less concentration of hormonal substance in the cortex, only recently has an extract been obtained which has been shown to maintain life in an adrenalectomized animal (Hartman,[18] Pfiffner and Swingle[29]). Still more recently, similar to the clinical recognition of other adrenal functions, a number of substances were obtained and isolated (Reichstein,[30] Wintersteiner and Pfiffner,[40] Kendall, Mason, and Myers[27]). Some were steroid in character and of androgenic potency. One of the first described adrenosterone (Reichstein[30]) had marked androgenic activity. Other steroids that have been isolated are in the process

of investigation as to their properties. Experimentally, the adrenal cortex has been shown to be of importance in many metabolic functions. Among the more important of these has been the regulation of the sodium and water content of the blood (Loeb, Atchley, Stahl,[23] Harrop, et al.[17]) and to be a factor in the amount of potassium present (Allers, et al.[1]). It has been suggested that it is a power in the regulation of the level of glycogen in the tissues

Fig. 3 *(left)*. C. R., a female, aged seventeen, with androtropic symptoms, hirsutism, acne, scanty menses and pain in right flank. A ten days' growth of hair on the face.

Fig. 4 *(right)*. Same case. Air injection radiograph of the adrenals shows very clearly a normal appearing left adrenal and indistinctly a right adrenal. This appeared normal on other exposures. Operation showed a normal right adrenal, hemi-section of which showed no pathologic changes.

(Evans,[14,15] Silvette and Britton[34]) and in the control of fat absorption from the intestine and the selective absorption of glucose (Verzar[39]). It has, in addition, been shown to have influence on the production of ammonia (Jimenez-Diaz[21]) and has some influence on the ketogenic factors (Long and Lukens,[24] McKay and Barnes[25]). From the multitude of experiments reported there are suggestions that the adrenals may also be implicated in many other metabolic processes. It has been shown, in addition, that there is a relationship between the adrenal cortex and the gonal-pituitary system and that hyperactivity of the ovary may partially replace adrenal function (Rogoff and Stewart,[31] Emery and Schwabe[13]).

In addition to the experimental evidence of adrenal cortical function, vitamin substances have been found to be present in the

adrenal cortex in comparatively large amounts; the first to be described as present was cevitamic acid or Vitamin C (Szent-Györgyi[38]).

Even with a short review of the experimental demonstration as to the possible various functions of the adrenal cortex, there appears to be some explanation as to the various bizarre changes as having been described in individuals with adrenal hyperfunction and possible hypofunction, when caused by tumors or other processes.

SYMPTOMS

Among the most frequently described syndromes of adrenal cortical hyperfunction are those of androgenetic character. Such symptoms in the female produce a progressive change of the secondary sexual characteristics towards adult masculinity. There is hypertrichosis of the male type, hypertrophy of the clitoris (towards penis), deepening of the voice, change in the body contour, change in the psychic outlook and behavior, and an associated depression of the female characteristics, as scanty or absent menses and diminution in size of ovaries and uterus. Less frequently are seen gynecotropic changes in a male with suppression of male characteristics and the development of feminizing trends, as hypertrophy of the breasts, atrophy of the testes and changes in body contour. These two trends apparently are directly due to the action of male sex hormones in the female and female sex hormones in the male.

Second among the syndromes has been the change towards adult maturity in children and the appearance of more rapid aging in the mature, a prematurity and presenility. In the sexual sphere the maturity is most often associated with the presence of male sex hormone (androsterone) in increased amounts over normal in the urine, and frequently the appearance of adult genitalia in male children is accompanied by a comparative lesser increase or no increase in the size of the testis compared with the penis. Accompanying the sexual mature appearance there is often present advanced dentition and closure of the epiphyses, as that growth ceases. As yet no material or extract has been obtained to show that this maturity feature may be due to a specific substance, but it has been suggested that this may be part of the result of the presence of excess androtropic material. The more advanced

aging seen in the mature is often associated with the other metabolism changes of skin, tissue, obesity, and edemas, changes more often seen normally in the aged.

In the third group, symptoms are various and at present are best classified as metabolic. They frequently resemble the many changes described by Cushing[12] and assumed to be often associated with basophilic adenoma of the pituitary. The changes in the

Fig. 5 *(left)*. L. G., female, aged twenty-seven, with metabolic syndromes (Cushing's type) and a left adrenal tumor. The photograph shows the moderate degree of facial hirsutism and the fatty cheeks.

Fig. 6 *(right)*. Same case. Air injection radiograph shows the mottled type of shadows due to the fibrotic fat, a large left adrenal is dimly made out. This was best shown by a composition of a series of exposures. The right adrenal is present and appears normal. The patient died of adrenal collapse after removal of the left tumor and autopsy showed the right adrenal as pictured, but the cells were atrophic.

skin are eruptions, pigmentation, dryness and loss of elasticity with striæ. In the hair, changes occur in color, texture, and distribution. There are increased deposits of fibrous fat in certain places, particularly the face, neck, and trunk, and depletion of the fat from others, particularly the extremities. The fatty deposits are often edematous. Changes occur in the blood, with apparent concentration of volume and cellular contents, with an apparent lessening of total blood volume in circulation but with high hemoglobin percentage, and red blood counts per cubic centimeter. There is often present a low sugar tolerance and the blood cholesterol readings have been uniformly high. Disturbances in the emotional field are seen in the well marked metabolism

syndromes. Bone changes appear to be less often present in the adrenal syndromes than in the somewhat similar ones due to pituitary changes. Whether such symptoms are caused by adrenal changes alone or are due to associated disturbances in other glands, a pluriglandular syndrome, appears to be debatable, but they are often seen with definite adrenal tumors.

Outside of the sphere of syndromes known to be associated with cortical tumors, are those definitely known cortical tumors which have occurred in both males and females without any recognizable hormonal changes. These tumors are cellular in type, resemble the apparent functioning cells of the normal adrenal but apparently produce no observed changes in the metabolism when present.

In an attempt to determine the status of the adrenal in fifty-nine cases studied at the Squier Clinic since 1927, a brief review is presented and such conclusions are given as may be drawn from the data available. The cases included all adrenal cortical tumors with or without endocrine symptoms and the adrenal-cortical syndromes with or without demonstrable tumors.

Among the fifty-nine cases were eight males and fifty-one females. There were six children, five males and one female. Among the fifty-three adults there were three males and fifty females.

There were two adult males with adrenal cortical tumors, one of which was a record of an autopsy case in which the patient succumbed from pulmonary metastases. The second, a male of thirty-six, had symptoms only of pain in his flank. He made an excellent recovery from the removal of his tumor. Later he complained of headaches occurring monthly, lasting four to five days, and apparently he excretes increased amounts of estrogenic substances in his urine during the headaches.

There were five male children, presenting prematurity or macrogenitosomia præcox, aged five, six, eight, eleven and eleven. The smallest three presented masculine prematurity of hair on genitals, body, and beginning on the face, associated with enlargement of the genitals but without appreciable enlargement of the testes. These children were larger than normal as far as growth was concerned, but showed no adiposity or other metabolism changes. Two showed no noticeable change in any hormonal gland and one showed a large left adrenal by air injection x-ray. The two boys,

aged eleven, showed marked hirsutism and hypertrophy of the genitals, including the testes, but their advancing maturity demonstrated itself by early fusion of the epiphyses with apparent shortening of the extremities; and with continued facial and muscular growth they resembled achondrodystrophic patients. One of these boys showed no apparent change in any hormonal gland, but the other had an apparent increase in size of his right adrenal. The

Fig. 7 *(left)*. M. H., female, aged twenty-eight, with androtropic and metabolism syndromes. Photograph shows hair distribution on her face. She excreted large amounts of male sex hormone in her urine.

Fig. 8 *(right)*. Same case. Air injection radiograph. Composite of series of exposures showed apparently normal size adrenals.

symptoms existed in both of these children over seven years, so that the syndrome may be present a long time with and without anatomic adrenal changes.

Two adult males were studied, one with most marked hirsutism, in whom there was no recognizable change from normal in the hormonal glands. The other had developed a silky hirsutism, obesity and diminution in the size of his penis and testes. A bilateral hypertrophy of his adrenals was shown by air injection x-rays.

There was one female infant with premature female maturity that showed no apparent change from normal in her adrenals by air injection x-rays.

Among the adult females, there was one patient with an adrenal cortical tumor without any obvious endocrine change. Her presenting symptom was pain in her side and her objective symptom

was a tumor mass. This was successfully removed, but death occurred one year later from metastases. Recently a similar case was called to our attention. The patient was never studied by us or operated upon, but on autopsy there was found a tumor similar to the preceding case.

By far the larger number of patients presenting symptoms suggestive of adrenal syndromes are adult females. Of the fifty

Fig. 9 *(left)*. E. S., female, aged thirty-two, with hirsutism, scanty menses, edemas, et cetera.

Fig. 10 *(right)*. Same case. An air injection x-ray shows a normal right adrenal. No left adrenal shadow could be demonstrated in several series of injections.

cases studied, the following tentative grouping was used: There were twenty-five cases presenting mainly masculinizing symptoms and with not sufficient evidence that there were any other hormonal changes present, with the exception of prematurity or presenility. Of these one had a tumor which was demonstrated by air injection x-rays and removed. Of the twenty-four remaining cases no tumor was demonstrated either by air injection x-rays or by operation in selected cases. Twenty-five cases presented hirsutism, virilism, obesity and other metabolism changes, four of which proved to have an adrenal cortical tumor. Of the remaining twenty-one, although presenting more or less similar symptoms to the four with tumor, we could not demonstrate adrenal changes by air injection x-rays or in some by operative exploration.

DIAGNOSIS

For the diagnosis of the anatomic condition of the adrenal, air injected into the perirenal fascial space was used in all the cases, after the manner previously described (Cahill,[7,9,10] Mencher[28]). The amount of air used varied with the size and type of individual: 200 c.c. or so in children, up to 500 c.c. in the obese adults. The injection of air visualized the adrenals so that their shadows were observed and attempts made to draw some conclusions from the shadows. This method, up to the present, appears to be better than any other, with the exception of operative exploration. Normal adrenals in thin individuals appear to show the clearer shadows. Encapsulated tumors in thin individuals throw clear shadows. Tumors that are attached to the liver or other structures show this attachment by air diffusing only part way around the tumor. In obese patients and especially those with symptoms resembling the Cushing syndrome, neither normal appearing adrenals, nor tumors visualize well, on account of the fat and fibrotic changes in the perirenal fascia. In such cases, the adrenal shadows may be determined by a composite from a series of radiographs as the air gradually diffuses through the fibrotic fat in the succeeding twenty-four or forty-eight hours after injection. In eight cases an adrenal shadow could be seen only upon one side.

In cases with androtropic syndromes there are excreted larger amounts of male sex hormonal substances than normal (Simpson,[35] Simpson, de Fremery, and Macbeth,[31] Gallagher,[16] Callow[11]) and the amount seems to vary with the degree of masculinization. Frequently these women excrete the amounts of female sex hormones seen in normal cases. Some of the patients with small androtropic changes and marked other metabolism changes excreted smaller amounts of both male and female hormonal substances than normal. Of particular additional interest has been the demonstration By Burrows et al.[5] and Simpson and Joll[36] of twenty times the normal amount of estrogenic substances in the urine of a male with adrenal cortical tumor and feminism. The large amounts of estrogenic material were accompanied by a moderately high amount of androgenic substances. The tumor was thought by them to have produced the excess estrogens because of the reduction to normal after removal of the tumor and the reappearance of an

excess associated with the recurrence as metastases. There also has been described a steroid compound isolated by Butler and Marrian[6] from the urine of a woman with adrenal genital syndrome and an adrenal tumor. It seems to be associated with the tumor syndrome because it is not excreted by men and by normal pregnant and non-pregnant women and it was not found in the urine after removal. Confirmation of this finding may be of great interest in the diagnosis of tumor. As yet, however, data on other types of tumor cases and investigation as to their hormonal excretions will be required before hormonal studies by themselves will establish the diagnosis of adrenal cortical tumor.

Of especial interest has been our investigation to determine the amount heredity seems to play in those cases of hirsutism, virilism, and other symptoms when present without tumor. As far as is possible to investigate the family histories in our shifting population, we have been convinced that such syndromes are not infrequent in these families. One particular family, four members of which were studied by us, two being sisters and the others second cousins unknown to each other, showed when traced that hirsutism occurred ten times among forty related people, and in addition three others had other endocrine pathologic changes. Other families examined showed somewhat similar tendencies and a separate report is to be made upon this subject.

PATHOLOGY

Most of the tumors were of a reddish-yellow color, ovoid in shape with a thin capsule. Although in none of our cases did the tumors invade other organs, two were attached to the under surface of the liver. According to the literature, the kidney has been the most frequent organ invaded. Sections from the males without endocrine symptoms showed irregular cells with very large and bizarre-shaped nuclei. These tumors showed a deep fuchsinophile reaction in the cytoplasm with the trichrome stain similar to that described by Broster and Vines[4] in adrenal genital syndromes. In the females without endocrine syndromes the cells resembled more the renal hypernephroma and looked most like the fasciculate layer of the adrenal and contained only small amounts of fuchsinophile granules. The androtropic tumor was an adenocarcinoma with considerable fuchsinophile granules in the cyto-

plasm and the cells mostly resembled the reticulate or inner layer of the adrenal. In the cases of androtropic and in Cushing type metabolism changes, the tumors were adenomas with uniform cells, or adenoma with large amounts of vacuolated cells or diffuse cellular carcinomas. These did not contain many fuchsinophile granules and it was not possible to tell from which cell layer the tumors might have been deprived. The syndromal cases without tumors that were operated upon had the adrenals carefully explored and in none was found any evidence of small adenomas. Portions of these adrenals were removed, selecting the thickest half of the larger glands in the hope that a small hyperfunctioning adenoma may have been in that portion. No adenomas were found microscopically and the gland structures were almost uniformly normal. Excess of fuchsinophile granules in the cytoplasm could not be demonstrated in the portions removed.

OPERATION

All the tumors were operated upon by the transperitoneal route. This permitted exploration of the entire abdomen and examination of the ovaries and the spermatic fascial planes where adrenal rests may occur. It allowed ligation of the vascular supply of the tumor before manipulation and theoretically should lessen dissemination. Exploration of the non-tumor patients, with the exception of two very obese, was also done by the transperitoneal route for better examination of the abdominal contents. Exploration of these obese patients through the flank was most difficult and exposure of the adrenals in 300- to 400-pound subjects was an almost impossible task.

In the tumor cases without syndromes, the silent growths had reached a large size and only their size made the technic of removal difficult. Two such patients made uneventful operative recoveries.

In androtropic tumors, the operative risk seems to be less than in those with other metabolism symptoms. The latter, with syndromes resembling Cushing's, frequently, after removal, quickly have shown signs of adrenal cortical failure and death. Similar end-results have been described in the literature. Recently Scholl[33] reported such an experience. Even though an opposing adrenal shadow may be demonstrated by x-ray and palpated and examined at operation, such adrenals apparently are frequently without

function. It has been suggested that in such tumors secreting possibly large amounts of hormone, necessary for plasma tone and function or other necessary life processes, cause by their oversecretion a functional or actual atrophy of the opposing adrenal. Support of this contention has been advanced in experiments, particularly by Ingle and Kendall,[20] who showed that administration of large amounts of cortin over a sufficient period of time to a normal rat will produce atrophy of both adrenal cortices. In addition, they have demonstrated that such an atrophy can be prevented by the administration of a fraction of an anterior pituitary extract which has high adrenotropic activity. Such experimental evidence suggests why collapse is less frequent in the sex type of tumor and suggests a preliminary course of treatment before operation in cases with multiple metabolism symptoms. Whether such injections will produce reactivity of functionless adrenal cells awaits demonstration. Three of our patients with metabolic type tumor went into collapse, two fatally; the third recovered, first thought to be due to the therapeutic measures used, but since she later died of metastases, our greater familiarity with the condition at that time led us to the probable explanation that she still had sufficient secreting tumor cells present to furnish the necessary life maintenance material.

The operative procedures in ten patients without tumors were followed by no complications and no fatalities. There were no signs suggestive of cortical failure.

DISCUSSION

Of three non-hormonal tumor patients, one was an autopsy case without operation, the second had the tumor removed successfully but died in one year from metastases, the third also had the tumor removed and is alive over a year but with unexplained syndromes and no evidence of metastases.

One patient with androtropic tumor has remained alive and well for over three years. These types, also judging from the literature, have a fair prognosis if operated upon early. There is usually a quick symptomatic recovery from the hormonal influence as far as the secondary sex organs are concerned if the patient is young, but no change in the fixed growth characteristics. The

change in the facial hirsutism has been slow and often unsatisfactory in those women who have shaved.

If a patient with androgenic and metabolic tumor survives removal, recovery from the hormonal changes appears to be slower. This may be influenced by the age incidence, such tumors occurring more frequently in adults. With a high percentage of malignancies among the tumor patients they are apt to succumb later with the original syndromes recurring with the metastases.

In the adrenal cortical syndromes that were mostly androtropic in type and without tumor, when there were scanty or absent menses, administration of female sex hormones not infrequently brought about restoration of the menses. In addition, Kurzrok showed that following the administration of the female sex hormones there was an apparent drop in the excretion of the male sex hormone. We have also seen, several times, the return of menses after an amenorrhea of a year or so, shortly after a bilateral air injection of the adrenal fascial planes. Operative diminution of the amount of adrenal cortex has also brought about the same change. A return of the menses or an improvement towards normal when not completely absent was not infrequent. There were in some an improvement of the typical configuration with increase in size of the breasts and buttocks. Neither hormonal therapy nor operative diminution in the amount of the cortex had much noticeable effect upon the hirsutism. Of the two it might be said that there was more apt to be a slight improvement following the operation. There was no change noticeable in the genitalia, voice or psychologic outlook.

Of interest has been the presentation by McQuarrie, Johnson, and Zeigler,[26] of their data on the electrolyte balance in the blood in a patient with Cushing's disease, which evidence they state upholds the contention of Bauer,[3] that this disease is essentially a state of hyperfunction of the adrenal cortex. Anderson and Haymaker,[2] with the same conception, treated two patients with a regimen of high potassium and low sodium (the opposite to Loeb's suggestion for Addison's disease), and with x-ray therapy in addition to the adrenal area, and they report a beneficial result in one patient. From their experimental evidence with animals they think that their results were indicative of the presence in the sera from humans with Cushing's disease, of a substance resembling the

adrenal cortical hormone. Our studies on the electrolytes in the Cushing type syndromes seen by us did not allow any definite conclusions to be drawn as to its relation to Addison's disease. We have no evidence as to the beneficial effect of dietary regimens. Several of our Cushing type patients with edemas and low blood pressures were given cortical hormonal extract, with disappearance of the edema in one case but with no change in the others. We may state that there was no change in the symptoms observed after x-ray therapy to the adrenals in non-tumor cases of the Cushing type or in those syndromes with known adrenal tumor metastases. The therapy of the non-tumor Cushing type appears to be in somewhat the same state of uncertainty as its causation.

SUMMARY

What are described as adrenal cortical syndromes are more frequently seen without any demonstrable adrenal tumor than with tumor. The syndromes more often have sexual changes towards adult masculinity (androtropic) in the female, and rarely a feminization of the male (gynecotropic). They also show a more rapid advancing towards maturity in the young (prematurity) or the appearance of more advanced age in the mature (presenility). There are also present in some general metabolism changes, more particularly in the plasma, skin, fat tissue, and in the psychologic status. In some cases one type may predominate; in others, all trends may be present.

For diagnosis, visualization of the adrenals by air injection x-rays was used to differentiate between tumor and non-tumor.

The excretion of male hormonal substances in the urine seems to vary with the sexual change and may be present in both tumor and non-tumor cases and may be reduced following removal of the tumor, or, if no tumor is present, may also be reduced following diminution of the adrenal cortex. There may be a specific hormonal substance excreted with some tumors.

The histology of the tumors varies. The androtropic tumor resembled mostly the reticulate layer. Fuchsin granules in the cells were present in both hormonal and non-hormonal tumors, but may be more predominant in the former.

The operative risk in androtropic tumors is less than in those with marked metabolic changes because, in the latter, atrophy

of the opposing adrenal appears to be frequent. The atrophy may have a pre-operative therapy.

Removal of the tumor produces a symptomatic cure but does not correct the fixed anatomic changes and the hirsutism often persists upon the face.

There are some apparently temporary symptomatic changes in the menstrual sphere in non-tumor cases following operative decrease in the amount of the adrenal cortex. There has also been some change in body contour and mammæ but none in hirsutism, genitalia, or voice.

REFERENCES

1. Allers, W. D., Nilson, H. W., and Kendall, E. C.: Proc. Staff Meetings Mayo Clinic, 11:283, 1936.
2. Anderson, E. M., and Haymaker, W.: Science, 86:2241, 545, 1937.
3. Bauer, J.: Klin. Wchnschr., 12:1553, 1933.
4. Broster, L. R., and Vines, H. W. C.: The Adrenal Cortex. London: H. W. Lewis, 1933.
5. Burrows, H., Cook, J. W., Roe, E. M. F., and Warren, F. L.: Biochem. Jour., 31:950, 1937.
6. Butler, G. C., Marrian, G. F.: Jour. Biol. Chem., 119:565, 1937.
7. Cahill, G. F.: Jour. Urol., 34:238, 1935.
8. Cahill, G. F.: New Eng. Jour. Med., 218:803, 1938.
9. Cahill, G. F.: Southern Surgeon (to be published).
10. Cahill, G. F., Loeb, R. F., Kurzrok, R., Stout, A. P., and Smith, F. M.: Surg., Gynec. and Obst., 62:287, (Feb. 15) 1936.
11. Callow, R. K.: Chemistry and Industry, 55:1030, 1936.
12. Cushing, H.: Pituitary Body, Hypothalmus and Parasympathetic Nervous System. Baltimore: C. C. Thomas, 1932.
13. Emery, F. E., and Schwabe, E. L.: Endocrinology, 20:550, 1936.
14. Evans, G.: Am. Jour. Physiol., 110:273, 1934.
15. Evans, G.: Am. Jour. Physiol., 114:297, 1936.
16. Gallagher, T. F.: Quoted by Cahill et al.[9]
17. Harrop, G. A., Soffer, L. J., Nicholson, W. M., and Strauss, M.: Jour. Exper. Med., 61:839, 1935.
18. Hartman, W. E., Dean, G. A., and McArthur, C. E.: Am. Jour. Physiol., 86:353, 1928.
19. Holl, G.: Deut. Ztschr. f. Chir., 226:277, 1930.
20. Ingle, D. I., Kendall, E. C.: Science, 86:2228, 245, 1927.
21. Jimenez-Diaz, C.: Lancet, 2:1135, 1936.
22. Lisser, H.: Endocrinology, 20:567, 1936.
23. Loeb, R. F., Atchley, P. W., and Stahl, J.: Jour. A.M.A., 104:2149, 1935.
24. Long, C. N. H., and Lukens, F. D.: Proc. Soc. Exp. Biol. Med., 32:743, 1935.
25. McKay, E. M., and Barnes, R. H.: Proc. Soc. Exp. Biol. Med., 34:682, 1936.
26. McQuarrie, I., Johnson, R. M., and Ziegler, M. R.: Endocrinology, 21:762, 1937.
27. Mason, H. L., Myers, C. S., and Kendall, E. C.: Jour. Biol. Chem., 114: 613, 1936.
28. Mencher, W. H.: Jour. A.M.A., 10:1337, 1937.
29. Pfiffner, J. J., and Swingle, W. W.: Endocrinology, 15:335, 1931.
30. Reichstein, T.: Helv. chim. acta, 19:223, 1936.

31. Rogoff, J. M., and Stewart, G. N.: Am. Jour. Physiol., 79:508, 1926-1927.
32. Rogoff, J. M., and Stewart, G. N.: Am. Jour. Physiol., 80:20, 1928.
33. Scholl, A. J.: Jour. Urol., 39:81, 1938.
34. Silvette, H., and Britton, S. W.: Am. Jour. Physiol., 109:98, 1934; Am. Jour. Physiol., 115:618, 1936.
35. Simpson, S. L.: Proc. Roy. Soc. Med., 27:383, 1933-1934.
36. Simpson, S. L., and Joll, C. A.: Endocrinology, 22:595, 1938.
37. Simpson, S. L., de Fremery, P., and Macbeth, A.: Endocrinology, 20: 363, 1936.
38. Szent-Györgyi, A. V.: Deut. Med. Wchnschr., 58:852, 1932.
39. Verzar, F.: Acta Brev. Nurland Phy. Phar. Microbiol., 6:50, 1936.
40. Wintersteiner, O., and Pfiffner, J. J.: Jour. Biol. Chem., 116:291, 1936.

ADRENAL PHEOCHROMOCYTOMA: THE SYNDROME OF PAROXYSMAL HYPERTENSION

REPORT OF A CASE AND RELIEF BY OPERATION

DAVID W. MacKENZIE and DONALD McEACHERN

From the Royal Victoria Hospital, Montreal, Canada

The syndrome of paroxysmal hypertension, due to chromaffin tumor, is dramatic and now well defined. The tumors responsible for these crippling seizures usually develop in the adrenal medulla, more rarely in retroperitoneal cell rests of chromaffin tissue near the adrenal. They are almost invariably well encapsulated and rarely metastasize. Secondary degenerative changes in the kidneys and cardiovascular system appear late and the diagnosis can often be made before such changes appear. Early removal of the offending tumor promises complete relief.

A considerable number of such cases of pheochromocytoma have been reported, the majority through their accidental discovery at autopsy. Since Labbe et al,[21] in 1922, drew the first clear picture of paroxsymal hypertension, a number of cases have been recognized clinically. Wells and Boman[42] have recently recorded eighty-two cases, of which twenty-seven were diagnosed during life. The condition may masquerade under the guise of petit mal, neurosis or atypical hypertension and thus remain undetected.

Review of the literature shows that some twenty patients (Table I) have been operated upon, including the one reported below. Five died from shock or complications. Fifteen recovered and have remained free of attacks.

CASE REPORT

J. R., male, aged twenty-nine, was admitted to Montreal Neurological Institute, Royal Victoria Hospital, May 6, 1937, as having a cerebral condition. Following consultation he was transferred to the urological department. He complained of paroxysmal attacks during the past fourteen months characterized by weakness, numbness in extremities, tight sensation in the chest and throbbing headache.

Seven months prior to onset of the present attacks, appendectomy was performed because of right lower abdominal pain of several weeks' duration. Recovery was uneventful, but the patient was readmitted

five days after discharge because of rather high fever. This gradually abated and he was discharged twelve days later with the diagnosis of infectious mononucleosis.

Present Illness.—In March, 1936, while skiing, the patient had a seizure of the type described below. This passed off in a few minutes. He remained well until May, 1936, when attacks recurred. They increased in frequency and severity and by July were occurring several times a month. For five weeks prior to admission, attacks were occurring many times a day and he was forced to remain in bed.

The following note made on admission describes the patient's symptoms:

"The attacks vary greatly, some being very mild, others severe. They are always of similar nature and usually follow physical exertion or emotional excitement. The first warning is a 'suffocating' feeling behind the sternum, a sensation that the heart is slowing and 'overworking,' but with no real palpitation or feeling of cardiac irregularity. A few seconds after onset his face blanches, there is mild, throbbing headache deep behind both frontal regions, and a severe throbbing superficial pain develops above the left eye. It abates and quickly disappears as the attack lets up. He has had no injury to this region. A sensation of coldness, numbness, tingling or tightness is felt first about the mouth, and then in succession in the left hand, left foot, right hand, right foot. It commences in the digits and spreads upward, depending on the severity of the attack, but is always more extensive on the left side. He has sometimes vomited but there is no desire to defecate nor are there rumblings of the gut or eructation of gas. There is invariably a desire to urinate although he can always control this. Consciousness is not disturbed at any time and he knows and remembers everything that goes on. The attacks last from three to twelve minutes, depending on their severity. Tinnitus and blurring of vision occur rarely."

Physical Examination: Temperature was 98.5; pulse 76; respiration 18. The patient was a well nourished, muscular man who looked in good health. The skin was pale but mucous membranes were of good color. The patient was intelligent and not emotional in his responses. There was a coarse tremor of the extended tongue and hands, which he claimed had been present all his life. There was moderate enlargement of inguinal and cervical lymph nodes.

The optic fundi were normal, the discs were clear cut. Retinal arteries were of normal caliber, not tortuous and did not compress the veins. There were no hemorrhages or exudates. The functions of the cranial nerves were normal throughout. There was no abnormality of tone, muscle power or coördination in the limbs. The tendon reflexes were equal on the two sides but somewhat hyperactive. Abdominal and cremasteric reflexes were diminished; plantar flexion both sides; unsustained clonus at both ankles. Thyroid was normal in size and no nodules were palpable. Lungs showed no abnormalities. Blood pres-

sure was 118/78. Heart was normal in size and position, rate 74 and regular, no murmurs or abnormal sounds. Abdomen showed no abnormal masses, nor tenderness. Liver and spleen were not felt. Skull and skeletal system were normal.

A tentative diagnosis was made of paroxysmal hypertension due to chromaffin tumor of the adrenal. Observation showed that each attack was associated with a rise of blood pressure parallel to the severity of the attack. The highest "spontaneous" elevation of blood pressure was 245/172. Between attacks the blood pressure was invariably about 120/80.

PRODUCTION OF ATTACKS: Although attacks sometimes occurred without apparent cause, precipitating factors were usually recognizable.

Fasting: There were apt to be numerous and severe seizures between 4 a. m. and breakfast and these were modified within a few minutes by glucose or orange juice. There was seldom one after breakfast save as a result of exercise. From 5 p. m. until supper was a bad period.

Posture and Activity: Almost any activity brought on seizures within a minute or two; e.g., getting out of bed, turning the trunk, lying on the left side or drawing up the knees. Movement or change of position of the head was not responsible. Elevation of the patient to the upright position, on a tilting table and with no muscular activity on his part caused a severe seizure. When a succession of attacks was produced, more intense and prolonged activity was necessary each time in order to obtain a given rise of blood pressure.

Abdominal Massage: On two occasions attacks were produced by deep massage over the adrenal regions. The patient lay flat on his back. Each time the more severe attack followed massage on the left side. Figure 1 illustrates one of these tests. Two minutes of massage on the right side caused an elevation of blood pressure to 170/110. One minute of massage on the left side produced a more severe attack and a rise of blood pressure which would have been greater had amyl nitrite not been administered.

Emotion: Paroxysms were apt to occur when the patient was tired, nervous or irritable, but he was better when entertained or having a good time with friends. The worst attack had occurred when a drunken man infuriated him. In the absence of physical exertion and before he could eject the intruder he became prostrated. This was a curious caricature of the normal adrenal defense mechanism.

DESCRIPTION OF ATTACKS: One to five minutes after one of the above procedures the patient would say, "It's coming." He was usually able to predict almost at once whether it would be a severe one. At the same moment the face and ears showed obvious and increasing

pallor, breathing became deeper and the radial pulse became slower and decreased in volume, while systolic and diastolic blood pressure rose rapidly. In severe attacks the pulse could not be felt at the wrist, though auscultation disclosed a regular heart beat which was forceful and pounding, the rate sometimes decreasing to 50 per minute. At the height of an attack the hands and feet were cold and pale, bluish or mottled, and marked coarse tremor of head, hands, and occasionally of feet, occurred. The patient was stoical both during and between attacks and there was no emotional display.

As the attack abated, the symptoms disappeared in reverse order, the pulse increased to normal rate and volume, the cardiac impulse became less forceful and occasionally a few extrasystoles appeared. The limbs became warmer, more moist and pallor diminished. No pupillary changes, flushing or profuse sweating were noted. Following an attack the patient felt weak and "jittery" and tremor of the hands, hyperreflexia and clonus at patellæ and ankles remained for many minutes.

The symptoms and hypertension usually reached their height about three minutes after onset, and abated two minutes later only to be followed by a secondary increase similar to that produced by epinephrine (Fig. 1). Attacks lasted from three to twelve minutes, the peak of blood pressure probably lasting but a few seconds. As many as eight and ten attacks occurred in the two or three hours before breakfast.

SPECIAL DATA

Skin Temperature was measured over the face, hands and feet and showed a consistent fall of about 0.5 C. to 1 C., in mild attacks, followed by increased warmth for a few minutes. Both during and between attacks the left side of the body was from 0.2 C. to 1. C. cooler than the right side over all areas tested. This was considered significant since numbness in the limbs was always earlier and more marked on the left side, presumedly because of increased sympathetic tone.

Carotid Compression: It was noted that compression of the left common carotid artery immediately relieved the pain above the left eye although the generalized "tight" headache was unaffected. The pain returned five to seven seconds after ending the compression. Compression of the right carotid was without effect. Massage of either carotid sinus region, between attacks, and with the patient standing caused no untoward symptoms nor change in pulse rate or volume.

Effect of Drugs: A few inhalations of amyl nitrite caused immediate temporary fall of both systolic and diastolic blood pressure (Figs. 1 and 3), and disappearance of symptoms. Sodium nitrite grs. 1 t. i. d. for four doses was of questionable value in reducing the severity of attacks. Perhaps this was an inadequate trial. Luminal and other sedatives were of no benefit.

Carbohydrate Metabolism.—The fasting blood sugar prior to an at-

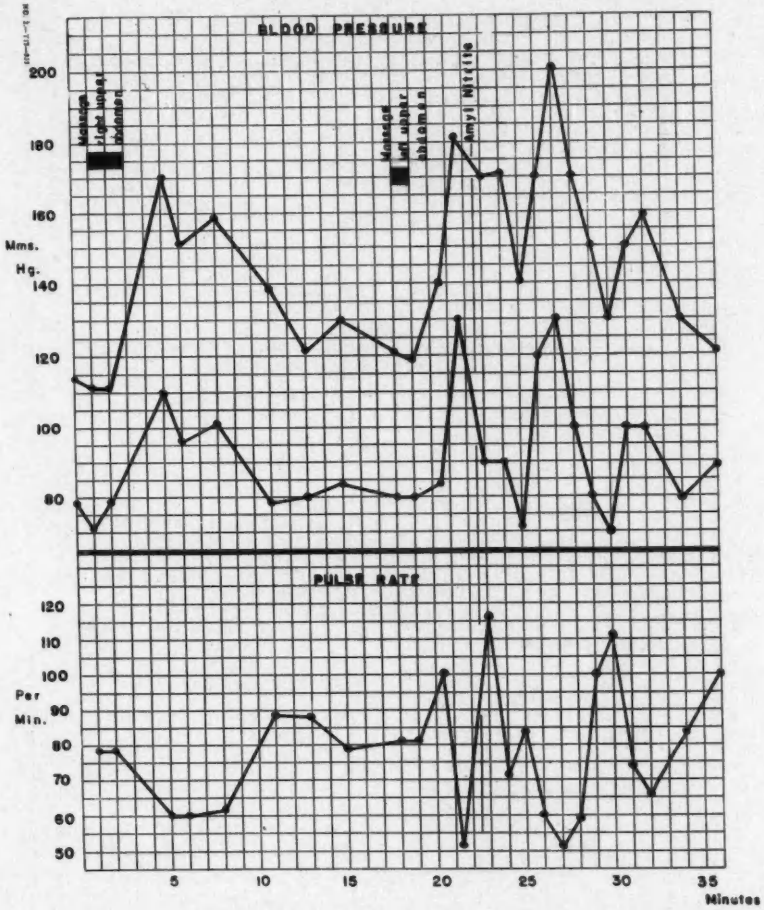


Fig. 1. Blood pressure and pulse rate during attacks produced by massage over right and left adrenal regions. The most severe attack followed massage on the side opposite the tumor. Note slowing of pulse with increase of blood pressure and effect of amyl nitrite.

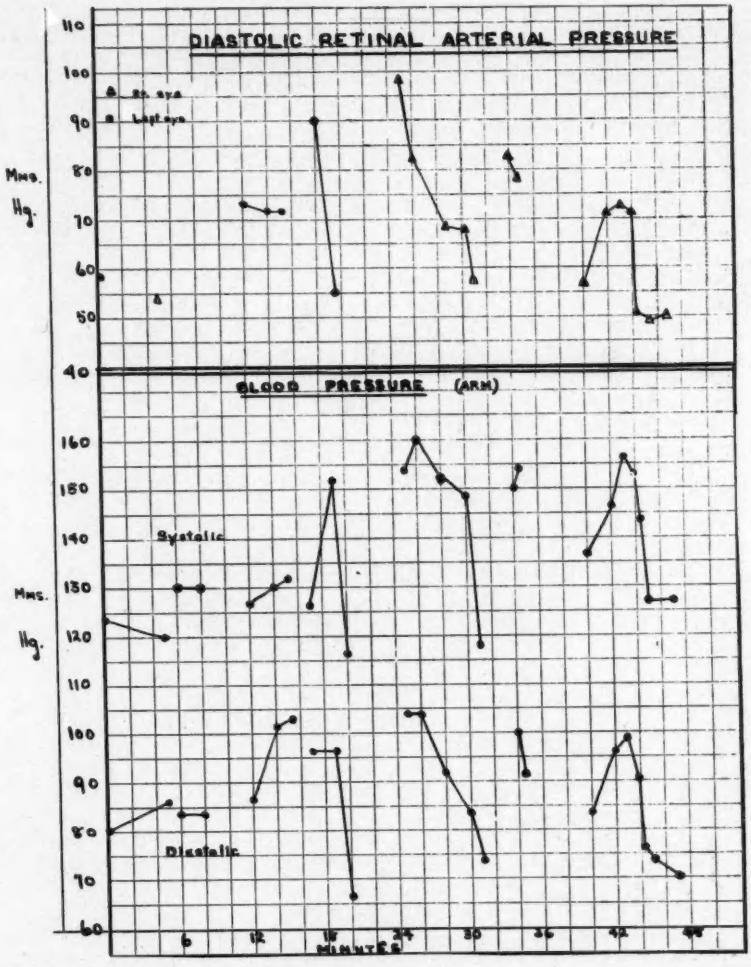


Fig. 2. Simultaneous determinations of diastolic blood pressure in retinal arteries and of brachial blood pressure during a series of attacks each of which was produced by bending the trunk forward. Determinations during first eight minutes were made prior to production of attacks.

tack was 100 mgs. per cent. A mild attack was then produced during which the glucose by mouth is tabled below. A series of preceding attacks were probably responsible for the high fasting value.

Time in Hours.	Blood sugar mgs. %.	Urine sugar gms. %.
0	133	Neg.
½	151	
1	184	
2	236	1.85
3	154	1.00

Mild glycosuria was apt to follow attacks. Two successive twelve hour specimens showed 34 mgs. per cent and 42 mgs. per cent of sugar respectively.

Electrocardiogram showed normal sinus rhythm, rate 90, normal A-V and intraventricular conduction time and no ventricular preponderance. T waves were of very low voltage and were inverted in leads I and II and diphasic in lead III. During a mild attack there was no significant change save that the rate fell to 60 per minute and no T waves were visible in lead I, while they were biphasic in leads II and III.

Retinal Arterial Pressure: The diastolic blood pressure in the retinal arteries was measured by the method of Bailliart.[2] These readings (Fig. 2), which presumedly mirror events in the cerebral arteries, show a definite parallelism to simultaneous changes in brachial blood pressure. No vasoconstriction was noted in the retinal arteries.

Blood Picture: Extensive studies of blood morphology, sedimentation rate, Van de Bergh, et cetera, were negative. Red blood cells, 5 million; hemoglobin 94 per cent. As shown below, the leukocytes increased during an attack.

	Attack-free		Attack	
	No. cells	Per cent	No. cells	Per cent
Polymorphonuclears	4,160	64.0	3,132	35.0
Lymphocytes	1,950	30.0	5,370	60.0
Mononuclears	326	5.0	448	5.0
Eosinophils	32	0.5		
Basophils	32	0.5		
WBCs	6,500	100.0	8,950	100.0

The above results were confirmed by recount. The change was therefore largely due to an increase in the number of lymphocytes with a moderate reduction of polymorphonuclears.

Additional Data: Urine (attack-free), S.G. 1010-1014; sugar and albumin, negative; microscopic, negative; phenolsulphonephthalein dye test, first hour 40 per cent, second hour 20 per cent. *Blood Wassermann, 0. Kahn, 0.* Basal metabolism rate (attack-free) 6 per cent. *X-ray of chest* was negative. Heart measurements normal. *X-ray of kidney areas* (plain): Lower pole of left kidney slightly lower than

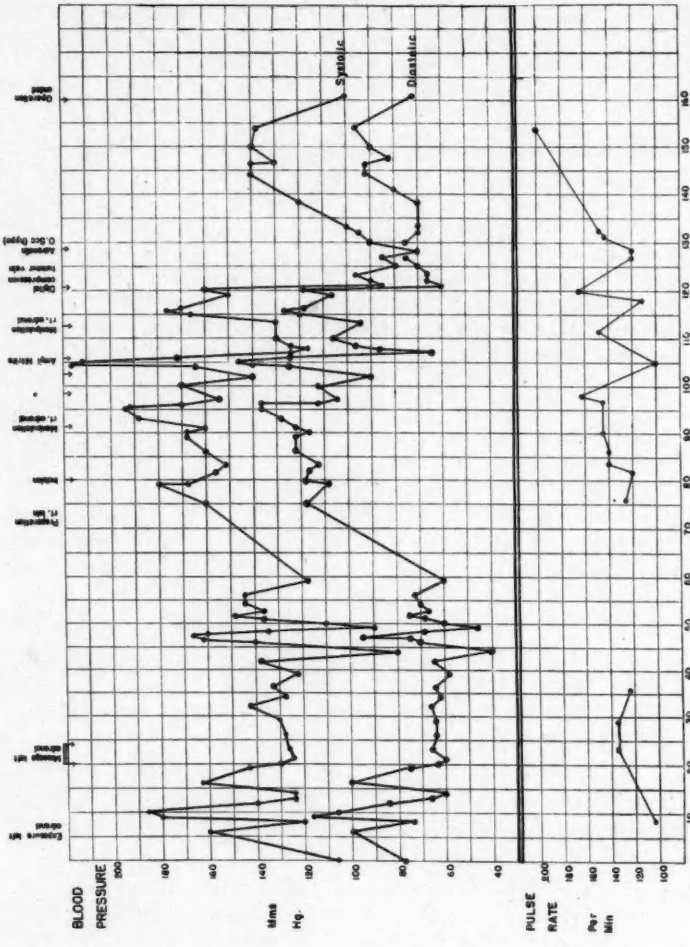


Fig. 3. Blood pressure and pulse rate during operation for removal of tumor. The various procedures are noted above. See text for full description.

that of right. Nothing otherwise remarkable seen. *Uroselectan series:* Right kidney relatively low, possibly some pathologic change at the upper calix. Left kidney in normal position but very large and with a congenital anomaly of two renal pelves, the upper one aplastic, the lower suggests some pathologic change. Retrograde pyelography was attempted but abandoned because of the severe attacks which ensued.

Operation.—It was difficult to determine the side of the tumor. On clinical grounds the left side was chosen, since lying on that side or massage there produced attacks more readily and since the lower pole of the left kidney was lower than normal. There was also a congenital abnormality of the left kidney, although this was recognized as a probable coincidence. The above points were without lateralizing value for the tumor was found to be on the right side.

Sodium nitrite was administered on the day preceding operation and intravenous glucose saline before and during its progress. Avertin (100 mgs. per kilo) was given by rectum and small amounts of ether and of N_2O and O_2 mixture to maintain a level of anesthesia. Amyl nitrite was at hand for inhalation through the vent of the mask if necessary.

Operative events are pictured in Figure 3. The left loin was opened by a lumbo-costal incision. Posturing the patient and exposure of the kidney resulted in several rises of blood pressure, perhaps due to pressure of the sandbag on the right loin. By the time the left adrenal was exposed, however, the blood pressure had dropped to normal. The adrenal was normal in size, shape and position. It was massaged and manipulated for several minutes and no change of blood pressure occurred. No adventitious glandular elements were found. The wound was closed.

The patient was repostured and the right loin opened. These preparations and subsequent manipulations caused rises in blood pressure which would have been greater had the surgeon not desisted until the pressure began to fall. Each rise was associated with brisk bleeding. The right kidney was relatively high and of the congenital variety, markedly lobulated and irregular. Above it, there was a large adrenal, and inside this organ a soft globular mass, slightly larger than a golf ball. The mass was easily freed from the adrenal cortex but this manipulation caused the blood pressure to rise to 212/146 and it fell precipitously on administration of amyl nitrite. When the large suprarenal vein was grasped with finger and thumb, the pressure dropped to 85/60. Freeing of the mass now caused no rise of blood pressure. The tumor was easily removed, the pedicle ligated and adrenal cortext left in position. Six minutes after compression and ligature of the vein the blood pressure was 80/70 and 0.5 c.c. epinephrine 1 :1000 was given subcutaneously. This caused a rise of pressure which was maintained until the operation was completed.

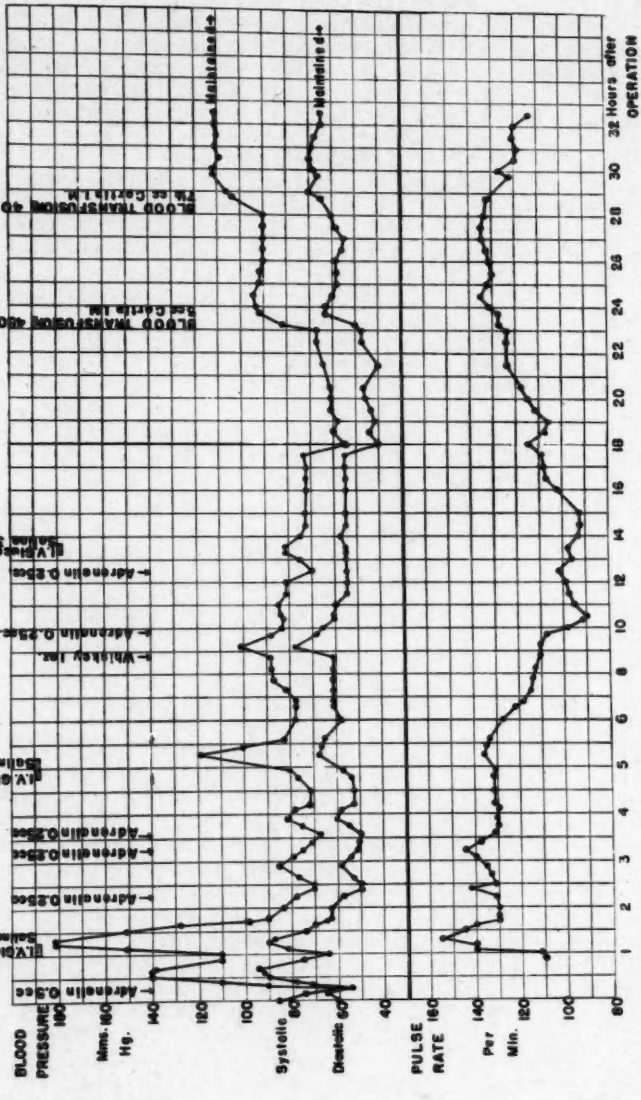


Fig. 4. Chart of early postoperative course. Epinephrine subcutaneously and glucose-saline intravenously were of temporary benefit during the first few hours, but later were ineffective. Transfusion of blood and intramuscular injection of adrenal cortical hormone caused immediate improvement which was maintained.

Postoperative Course.—During the first six hours after operation either intravenous glucose-saline or epinephrine subcutaneously raised the blood pressure from 80/60 to a satisfactory level for about thirty minutes, but this became less and less effective. Finally the blood pressure remained unaffected by these procedures. Twenty-four hours after operation the blood pressure was 60/45, pulse 120, heart sounds of tic-tac quality. There was profuse perspiration, the skin was cold and the picture one of shock. The patient was voiding well. Changes in blood pressure and pulse rate are shown in Figure 4.

It was thought that there might be temporary adrenal cortical deficiency due to manipulation of both glands. Transfusion of 450 c.c. citrated blood and intramuscular injection of 5 c.c. adrenal cortical extract caused immediate improvement and the blood pressure rose to 110/60, which was maintained. Cortin was administered for several days.

No further attacks occurred following operation and the blood pressure remained normal. The patient was discharged one month after operation, at which time his blood pressure was 118/76. Examination showed no abnormality save for the generalized pallor and coarse tremor of the hands, which was less marked.

Seven months after operation the patient reports himself completely well. There has been no attack since operation. The tremor of his hands disappeared. The blood pressure is 120/80.

Description of tumor. "The tumor weighs 24 gms. The capsule is thick, smooth, gray and fibrous. The tumor material is soft and hemorrhagic with some greyish areas."

Microscopic.—"The capsule encloses a solid growth of tumor cells, between which there is very little stroma except for numerous capillaries. The cells consist of two main types. The larger cells are polygonal with abundant cytoplasm, and contain a large oval nucleus, with numerous fine granules which tend to be basophilic. Between these cells are smaller, more angular, dark staining cells which have compact acidophilic cytoplasm and smaller dark staining nuclei, in which the nucleoli are not obvious. Transitions between the two forms are numerous. In one area a large collection of tumor cells lies free in the lumen of a vein. It is impossible to be certain whether this has resulted from ingrowth or is due to an artefact. Stains for iron are negative. Chromaffin and fat stains could not be made.

"*Diagnosis:* Paraganglioma (pheochromocytoma)."

Epinephrine Content.—Determination by the method of Folin, Cannon, and Denis[13] showed the presence of 0.38 gms. of epinephrine per 100 gms. of tumor tissue. The presence of this large quantity was confirmed by biologic assay on the decerebrate cat. The normal adrenal gland contains from 4 to 5 mgs. epinephrine.[38]

TABLE I. SUMMARY OF CASES

Author	Age	Sex	Duration of Symptoms	Phenomena During Attack	Duration of Attacks	Blood Pressure		Heart Rate Attack	E. K. G.
						Usual	Attack		
Masson & Martin[26] 1923	45	F		Right abdominal pain. Attacks of suffocation.					
Mayo[27] 1927	30	F	1½ yrs.	Palpitation, headache nausea, vomiting, tremor, apprehension, numbness hands and feet, visual symptoms. Sweating, abdominal pain. Pulmonary edema.	¼ to 4 hours	130/82	320/180	Moderate increase	Normal. change ing attac
Pincoffs & Shipley[30 37] 1929	25	F	10 yrs.	Fulness chest, headache, nausea, vomiting, tremor, apprehension. numbness hands, face, feet. Pallor. Albuminuria, glycosuria, tachypnea. No pressor substance found in blood.	1 to 3 hours	120/80	260+/110+	Increase to 110	Normal ty of ar mias an wave ch during tacks.
Porter & Porter[42] 1930	39	M	2½ yrs.	Nausea, vomiting, apprehension, pallor.	1 to 4 mins.	110 syst.	200+ syst.	Decrease to 55	
Lazarus & Eisenberg[23] 1932	53	F	1½ yrs.	Epigastric distress, pyrosis lumbar pain, hematuria, pyuria, dysuria. No typical attacks.		156/106			
Volhard[41] 1931	33	M	1½ yrs.	Dizziness, headache, pallor, sweating, albuminuria.		180/120	300/170		
Planteydt & Suermondt[39]	23	M	2 yrs.	Fulness and oppression chest, pallor, sweating	Few mins. to 3 hours	134/110	325/200		
Belt & Powell[4] 1934	45	F	2 yrs.	Headache, dizziness, nausea, vomiting, sweating visual symptoms, pallor, palpitation albuminuria, glycosuria, pulmonary edema. Numbness hands.	Several hours	170/80	300+/240	Increase to 135	Sinus t cardia d attack.
Leriche,[24] Bauer[20] 1934	41	M	1½ yrs.	Palpitation, nausea, vomiting, tremor, bladder and bowel hyperactivity. Pulsation eyeballs. Numbness hands and feet. Pallor, albuminuria, glycosuria.	1 to 1½ hours	200/105	340/110	Decrease	
Coller et al.[8] 1934	16	M	5 mos.	Headache, nausea, vomiting, tremor, sweating, numbness hands and feet, pallor, albuminuria, pulmonary edema. Epigastric pain.	Few mins. to several hours	125/105	300/220	Decrease	Sinus t cardia version T₂. No E during
Kalk[16] & Büchner[6] 1934	36	F	9 yrs.	Headache, palpitation, oppression in chest, anxiety, pallor, dilatation of pupils.	Few mins. to several hours	125/85	300+	Increase	

CASES

ICH OPERATION HAS BEEN ATTEMPTED

E. K. G.	Laboratory Data	How Tumor Demonstrated	Tumor Location	Tumor Size	Operative Approach	Postoperative Course Immediate	Postoperative Course Late
			Above kidney right.	Large kidney.		Severe shock. Death in 6 hours.	Death.
Normal change ng attac	ndary anemia. Nail capillaries obliter- during attacks.	Palpation—yes Operation—yes	Near adrenal left	6 x 4 cms.	Midline abdominal.	Usual. Pulmonary infarct 3rd week.	Well 7½ years later.
Normal ty of ari mias an wafe cha during acks.	hypersensitive to nalin. Blood sugar nal. 160 mgs. per during attack.	Palpation—no Operation—yes	Adrenal right.	Kidney 150 gms.	1st op.—left rectus. 2nd op.—right costal margin.	Severe shock 12 hrs. Transfusion.	Well 6 years later. B.P. 110/70
	B.C.'s 14-20,000. derate renal insuf- ency.	Palpation—no Operation—yes	Adrenal right.	Globular	Mid-line abdominal extended to right.	Severe shock 24 hrs.	Well 4½ years later.
	aces of albumin, B.C.'s and W.B.C.'s urine.	Pyelography—yes Operation—yes	Adrenal left.	8.5 x 6 cms.		Not unusual.	Well.
		Palpation—no Operation—no Autopsy—yes	Adrenal right.	Hen's egg.	Left adrenal 3 x normal size. Removed. Tumor right side at autopsy.	Slight fall in B.P. Hyperpyrexia. Coma 2 days.	Death.
	cose curve 1-0.93, 08, 3-0.73. Renal ction normal.	X-ray—yes Operation—yes	Adrenal right.	149 gms. 10 x 7 x 4 cms.		Marked hypotension for 2 days.	Well 6 months later. B.P. 110/80.
Sinus t cardia d attack.	B.C.'s 10, 200.	Palpation—yes Pyelography—yes Autopsy—yes	Adrenal right.	1000 gms.	Spinal anesthesia. Operation deferred. Shock.	Coma for 2 days.	Death.
	od sugar before at- , 124 mgs. per cent. od sugar—during at- , 225 mgs. per cent.	Palpation—no X-ray—no 1st Op.—no 2nd Op.—yes	Near adrenal left.	Large cherry.	Previous exploration wrong side. Second operation with removal.	Not unusual.	Well 6 months later. B.P. 140/100.
Sinus t cardia. version T_3 No E during a	od sugar normal dur- attack. posensitivity to ad- alin.	Palpation—no X-ray—no Pyelography—no Operation—yes	Adrenal right.	8 cms. diam.	Mid-line abdominal extended to right. Ether anesthesia. Previous attempt with $NO+O_2$—collapse.	Collapse restored by transfusion.	Well 6 months later.
	od sugar 110 mgs. cent. No change ng mild attack. Nor- after operation.	Palpation—no Massage over tumor—yes Pyelography—yes Operation—yes	Adrenal right.		Right paracostal, transperitoneal.	Not unusual. Later-pneumonia.	Well.

TABLE I. SUMMARY OF CASES

Author	Age	Sex	Duration of Symptoms	Phenomena During Attack	Duration of Attacks	Blood Pressure		Heart Rate Attack	E.K.
						Usual	Attack		
VanGoidsenhoven Appelmans[40] 1934	35	F	1½ yrs.	Pallor, tremor, sweating, palpitation, nausea, vomiting, left lumbar pain. Epigastric pain. Weakness, albuminuria.	Several mins.	130/90	240/150	Increase	
Kelly et al.[17] 1936	37	F	7 yrs.	Palpitation, fullness in head, nausea, vomiting, tremor, weakness, epigastric pain, sweating, visual symptoms, anxiety, numbness hands and feet, pallor.	5 to 10 mins.	120/75	280/160	Slight increase	Normal phasic attack
Beer et al.[3] 1937	26	F	9 yrs.	Nausea, headache, palpitation, pulsation neck vessels, dyspnea, numbness and pallor, cyanosis digits, sweating, weakness, tremor.	5 mins.	140/100	280/200	Increase	Leftwe prepon ance. Si wavech
Mackenzie & McEachern 1938	29	M	1⅓ yrs.	Palpitation, substernal oppression, occasional nausea. Numbness extremities and face, pallor, tremor, hyper-reflexia, desire to micturate, headache, weakness, glycosuria.	3 to 12 mins.	120/80	245/172	Decrease to 50	Normal changes ing atta
McKenna & Hines[25] 1935	59	F	1½ yrs. +	Precordial palpitation.		162/80			
Landau et al.[22] 1936	32	M	4 mos.	Headache, salivation, nausea, vomiting, abdominal cramps, pallor, coldness limbs, oppression chest, pulmonary edema, hyper-reflexia, coarse tremor limbs and head, dilatation and inactivity of pupils, disappearance dorsalis pedis pulse, sweating, exhaustion, glycosuria albuminuria.	Up to 5 hours	100/70	270/140	Increase to 100	
Pincoffs (See Howard & Barker)[18] 1937	45	M	7 mos.	Renal colic, headache nausea, dyspnea, sweating, pallor and coldness of extremities, glycosuria, albuminuria, cylinduria.	1 to 10 hours	140/90	260/150		
Burgess, Waterman and Cutts[7] 1936	27	F	4 yrs.	Headache, palpitation, nausea, vomiting, pulmonary edema, pallor, cyanosis, distention neck veins, contraction pregnant uterus, glycosuria.	Several minutes to several hours	120/80	240/180 (65/40 after attacks)	Decrease and irregularity	Nodal systoles ing atta
Binger & Craig[5] 1938	29	F	3 yrs.	Constant headache, palpitation, dyspnea. No attacks. B. P. varied between 290/120 and 120/78.					Normal

HICH OPERATION HAS BEEN ATTEMPTED (Cont'd)

Laboratory Data	How Tumor Demonstrated	Tumor		Operative Approach	Postoperative Course	
		Location	Size		Immediate	Late
R.B.C.'s 8.600. Polys—%, Lymphs—37%, nos—10%. Bl. Cho-terol 226 mgs.%. Glu-se curve 0-95 mgs.%, -183 mgs.%, glycosu-, 2-90 mgs.%.	Palpation—no X-ray—no Peritoneal pneumogram—yes Operation—yes Pyelography—yes	Adrenal left.	135 gms. 8 x 6 x 6 cms.	Lumbocostal, left.	Severe shock 12 hrs. Restored by transfusion.	Well 6 months later. B.P. 130/80. Blood cholesterol 150 mgs. %
P. response to cold t normal. ood sugar 90 mgs.%. uring attack, 118 mgs	Palpation—yes Operation—yes	Adrenal right.	240 gms. 8.5 cms. diam.	Right postero-lateral.	Not unusual.	Well 4 months later. B.P. normal.
ood sugar 175 mgs.%. Cholesterol 425 mgs. B.M.R. +69, +39, 27. Glucose curve 5 mgs.%, 1-240 mgs. , 1-50 mgs.%. Hyper-nsitive to adrenalin d insulin. Demonstra-n of pressor sub-nce in blood.	Palpation—no X-ray, pyelography, perirenal insufflation, operation—yes	Adrenal left.	290 grams. 9 x 9 x 6 cms.	Left lumbar. Preliminary left kidney.	Moderate shock.	Well. B.P. 125/85. B.M.R. + Bl. Chem. normal. No pressor substance in blood.
ucose curve 0-133 mgs. 2-236 mgs.%, 3-154-s.%. Lymphocytosis ring attack.	Palpation—no X-ray—no Pyelography—no Massage of tumor—no Operation—yes	Adrenal right.	24 gms. Golf ball.	1st—incision, left lumbar. 2nd—incision, right lumbar.	Moderate shock. B.P.	Well 11 months later. B.P. 120/80.
.B.C.'s 11,200.	Palpation—yes Pyelogram—yes Operation—yes	Adrenal right	12x11x9 cms.	Right lumbo-costal with nephrectomy.	Not unusual.	Well on discharge. B.P. 96/48.
ood (arterial) sugar erval 79 mgs.%; at-k 289 mgs.%. ucose curve immedi-ly after attack, 0-236 s.%, ½-289 mgs.%, 89 mgs.%, 2-129 s.%, 3-79 mgs.%. ukocytosis 19,000 ring attack. B.M.R. er attack, +34%. od Wass. positive.	Palpation—no X-ray—no Operation—yes	Near adrenal right.	Hen's egg.	Left abdominal paramedian.	Not unusual. B.P. normal. No further attacks.	Broncho-pneumonia. Death after 30 days.
od sugar during two cks, 192 mgs.% and mgs.%.	Operation—yes	Near adrenal right.	4.5 x 4 x 3.5 cms. Wt. 28.5 gms.		Shock and collapse.	Well.
od sugar 125 mgs.% l 110 mgs.% (both ting). N. P. N. 31 s.%, 29 mgs.%. roscopic examina-n of heart during ack.	Palpation—yes Pyelogram—yes Operation—yes	Adrenal right.	9 cms. diam.	Right rectus with lateral extension.	Shock. Collapse. Pulmonary edema.	Death in 3 hours.
M.R. before opera-, +61%. M.R. after operation, 1%.	Palpation—no 1st op.—no 2nd op.—yes	Adrenal right.	6x6x3.5 cms.	Adson approach for splanchnectomy.	Pulmonary congestion.	Well. B.P. 140/90.

DISCUSSION

Of forty-two cases of adrenal chomaffin tumor collected by Belt and Powell,[4] nineteen were male, twenty-one female and in three the sex was not stated. The tumor was on the right side in seventeen, left side in sixteen and bilateral in eight instances. The tumors varied from the size of a pea to one weighing 260 gms. Eight cases were complicated by other neoplastic growths, including malignant pheochromocytoma with metastases, hypernephroma, neurofibromatosis, et cetera. These cases were mostly from autopsy material and twenty-seven lacked clinical data which might now enable us to distinguish the simple chromaffin adenomas. The frequency of bilateral tumors is worthy of note. The youngest patient was two and one-half years, the oldest eighty-two.

Edward[10] has recently tabulated data on fifty-two cases; twenty-two occurred in males and thirty in females. Of forty-nine cases the tumor was on the right side in twenty-eight on the left side in eleven and bilateral in ten. The incidence in young adult life is shown by the fact that forty-five of fifty-one patients were between the ages of ten and fifty. Most of these tumors were found at autopsy.

Gärtner's review[14] of twenty-two cases of paroxysmal hypertension gives a clearer picture of the condition. There were twelve males, nine females, and one not stated. The tumor was on the right side in ten, left side in three, bilateral in four and location not stated in five instances. The patients varied in age from eighteen to seventy-two; all but two were between the ages of eighteen and forty-nine. No cases of malignancy were noted.

The best clinical discussion is found in the recent paper of Howard and Barker,[15] who analyze the symptoms and findings in eighteen well documented cases of paroxysmal hypertension. The French literature contains an excellent symposium introduced by the paper of Donzelot.[19]

Table I summarizes the cases in which operation has been attempted. These tumors usually give rise to symptoms in the third, fourth and fifth decades, but children may be affected. The frequent occurrence of the tumor on the right side is important.

Paroxysmal Hypertension.—The attacks suffered by our patient were similar in most respects to others described in the literature. Palpitation, sense of suffocation, headache, numbness and cold-

ness of the extremities and coarse tremors are the rule. Nausea, vomiting and epigastric distress often usher in a seizure. The heart beat is strong and over-demonstrative. It may be slow or may increase sufficiently to suggest paroxysmal tachycardia, and extrasystoles are apt to appear. The pulse in radial or dorsalis pedis arteries may diminish in volume or vanish due to vasoconstriction. At the height of an attack pulmonary edema sometimes occurs with frothy, blood-stained sputum and other signs of cardiac embarrassment. The patient is often tremulous and apprehensive. Suffusion of the skin and drenching sweat usually follow an attack.

Attacks are of all degrees of severity, from the merest warning of discomfort to the most prostrating seizure. Phenomena more rarely described include: Dimness of vision or flashing lights, precordial pain, enlargement of neck veins, desire to micturate, exophthalmos, dilatation of pupils and dizziness or tinnitus. Disorders of consciousness and epileptiform seizures have occurred in a few instances. Crampy abdominal pain may be a prominent feature or paroxysms of pain in the affected loin. Tachypnea and respiratory hyperventilation leading to alkalosis and tetany occurred in one case.[16]

Attacks usually last but a few minutes but they may persist for hours. Leukocytosis and increase of urea and cholesterin in the blood is sometimes noted. The blood sugar may or may not be elevated. We suspect that hyperglycemia would be found often were the blood examined at the proper moment during or after these fleeting seizures. These patients are apt to lose weight despite a normal or increased appetite for food. During attacks oliguria and increase of blood urea may occur followed by polyuria, cylindruria, mild hematuria, and a drop of blood urea. Glucose and albumin usually appear in the urine after attacks. Electrocardiograms in the few recorded attacks have shown either no change or a variety of temporary abnormalities, including auricular and ventricular extrasystoles, ventricular tachycardia and inversion of T waves in leads I and II.

Persistent Hypertension.—With the passage of months or years the attacks increase in frequency and severity. In older subjects or in young subjects who have had attacks for a long time,[18] permanent vascular and renal changes occur. The blood pressure remains high at all times and the elevations associated with at-

tacks are superimposed. Cardiac hypertrophy, arteriosclerosis, retinal changes, persistent albuminuria and other evidences of renal involvement appear. Such cases offer the greatest difficulty in diagnosis since the picture is predominantly one of cardiovascular renal disease while the history or continued occurrence of paroxysms is overshadowed. Many such cases are described in the older literature, the presence of adrenal chromaffin tumor having

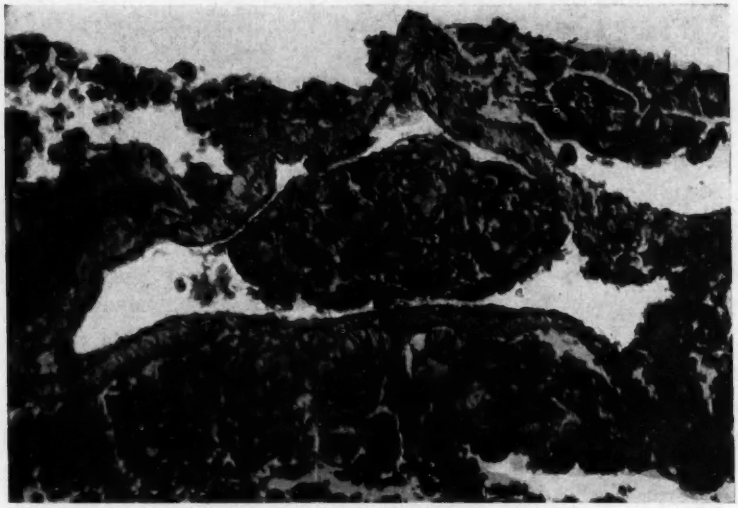


Fig. 5. Photomicrograph showing tumor cells within a blood vessel, the wall of which is intact. This occurrence has been described before (see Rabin[24]), but may be an artefact.

been discovered at autopsy. Death usually resulted from cerebral hemorrhage, uremia or cardiac decompensation. In the case to be reported later, a girl of twelve had suffered from persistent hypertension, renal changes and megacolon for at least four years. Death occurred from air embolism during an attempt to visualize the adrenals by perirenal insufflation of air. Autopsy revealed bilateral adrenal medullary tumors. The case recently reported by Binger and Craig[5] is of great interest. The picture was that of essential hypertension, but bilateral splanchnectomy caused no fall of blood pressure. Removal of an adrenal tumor resulted in

disappearance of the hypertension. This shows that a pheochromocytoma may cause persistent hypertension for which permanent vascular or renal changes are not responsible.

Such cases have served to keep alive the theory that hyperepinephrinemia is a cause of certain types of hypertension of cardiovascular renal disease. If a tumor can produce the picture it seems possible that hyperplasia or increased functional activity may do so. A number of authors have pointed out the similarity of the morbid changes to the arteriosclerosis produced in animals by epinephrine (see Oppenheimer and Fishberg[28]).

Diagnosis.—The diagnosis is established by the character of the attacks described above and is confirmed by blood pressure readings made during and between attacks. It is obviously desirable to make repeated routine blood pressure determinations and to observe attacks induced in the requisite manner. The paroxysms are distinguished from petit mal and other epileptic seizures by their variable but graded severity, by the wide variety of vascular and other autonomic phenomena and above all by preservation of consciousness. The rare type of autonomic diencephalic epilepsy, first described by Penfield,[29] might prove confusing, but there would usually be other evidence pointing to a cerebral lesion. The numbness of extremities, hyperreflexia and spasmodic nature of attacks may suggest the picture of tetany, but this condition should be easy to exclude. Intermittent elevation of blood pressure, sometimes extreme, has been observed associated with eclampsia, lead colic, mediastinal tumor involving the vagus nerve, irritation of the trigeminal nerve and during the gastric crises of tabes. The attacks due to adrenal chromaffin tumor have a different character and can best be likened to the effects of epinephrine, which indeed we believe to be their cause.

Persistent hypertension is frequently found in association with tumors of the adrenal cortex. These tumors, however, are usually large and highly malignant. They occur most often in children along with hypertrichosis, virilism and other evidences of precocious sexual development. The latter phenomena are not seen in uncomplicated cases of pheochromocytoma.

Determining the side of the tumor may be difficult. Many of the tumors are so small that they cannot be palpated and since they do not tend to calcify they may neither cast a shadow nor

cause displacement of the kidney shadow in plain roentgenograms. Pyelograms have shown the presence of tumor in several cases but more often have failed. Von Goidsenhoven and Appelmans[40] demonstrated a tumor weighing 135 gms. by peritoneal pneumography and this may prove a valuable aid. A large neoplasm was visualized by Beer et al[3] by perirenal insufflation of air. We have used this method several times to exclude adrenal tumor in unusual

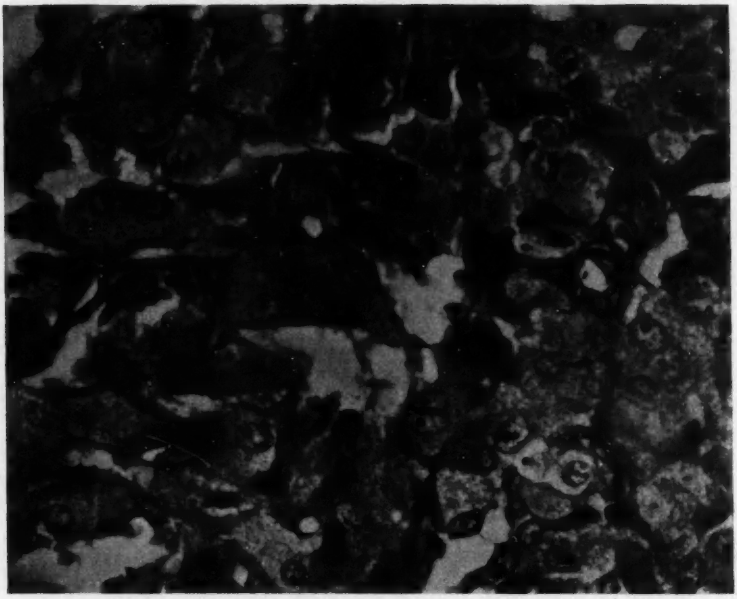


Fig. 6. Photomicrograph of tumor showing variability of cell structure and staining reactions.

cases of hypertension. The possibility of bilateral tumors should always be kept in mind.

Kalk and Büchner[16,6] were the first to produce attacks by deep massage of the neoplasm. This procedure led us astray, although it is possible that frequent repetition would have correctly indicated the side of the tumor. This we were loath to do because of the reputed vascularity and necrosis of these growths. They are well encapsulated, however, and the procedure may be of great

value if used with caution. We are aware of one instance in which routine palpation of the abdomen resulted in a fatal seizure, the tumor being discovered at autopsy. When the condition is suspected, this danger can be minimized by starting with brief and light massage and allowing time for development of the attack before proceeding further.

In two recorded cases the attacks were more severe and frequent when the patient lay on the affected side. The opposite was true in our case. It is not always a simple matter of compression of the tumor, and local vascular changes may play a rôle. Severe attacks were produced in our patient by changing his position from horizontal to upright on a tilting table, with no physical effort on his part.

Treatment.—Removal of the tumor abolishes the attacks of hypertension. No attacks have occurred after operation in any of the instances of successful removal.

Von Goidsenhoven and Appelmans[40] report the cases of Mayo,[27] of Shipley,[37] and of Porter and Porter,[43] as completely cured seven and one-half, six, and four and one-half years respectively after operation.

X-ray therapy has been unsatisfactory save for temporary improvement in one case.

The operative approach will necessarily vary in different cases. If the side of the tumor is known and if its size and position have been determined by palpation, x-ray or other procedures, there are many points in favor of extraperitoneal intervention by lumbar incision. When exploration is necessary to localize the tumor there may be advantages in employing a ventral midline incision which can be extended laterally to expose the lesion (Table I).

Spinal anesthesia seems to be contraindicated and any degree of asphyxia should be avoided if nitrous oxide-oxygen mixture is used. Basal anesthesia with avertin along with small amounts of ether and nitrous oxide-oxygen mixture proved satisfactory in our case.

Preparations for blood transfusion and intravenous glucose-saline injections should be made beforehand. The necessity of repeated blood pressure determinations during and after operation cannot be overstressed. In our case (Fig. 3) the periods of rising pressure were signals to the surgeon to desist until the pressure

began to fall. Inhalation of amyl nitrite was necessary to control one threatening rise of pressure. Manipulation of the tumor should be held to the minimum; the veins draining it should be ligated at the first opportunity.

Management of Attacks.—Severe attacks are a real cause for concern. The danger of cerebral hemorrhage, pulmonary edema or some other complication is ever present.

The nitrites appear to be a logical choice to combat attacks. Their vasodilator action is peripheral and they antagonize the vasoconstrictive effect of epinephrine. Mayo[27] could note no benefit from "nitrites" and no improvement was seen in our case with a short trial of sodium nitrite. Persistent and adequate use of nitroglycerin or sodium nitrite might be helpful. It seems better, however, to use inhalations of the rapidly acting amyl nitrite for individual attacks that are of short duration. This proved effective in our case and in the cases of Shipley[37] and Labbe et al.[19] The patient should be reclining to guard against snycope. Ergotamine and various forms of sedatives have proved useless. Morphine caused some retardation and amelioration of attack in the case described by Landau et al.[22] Frequent feedings of a high caloric diet seem indicated in view of the glycogenolytic action of epinephrine. Such feedings reduced the number and severity of attacks in our patient.

These patients bear surgical and other procedures poorly. Childbirth, hemorrhoidectomy, local application of cocaine for tooth extraction, simple amputation of a gangrenous extremity and operation for the adrenal tumor itself have been responsible for death, preceded by the signs of shock and collapse. The blood pressure falls to very low levels, there is clammy sweat, pallor, thready pulse and tic-tac heart sounds. This may follow removal of the tumor or other unrelated trauma, or it may follow the ordinary hypertensive episodes with no trauma whatever. The mechanism of these episodes has been likened to the hypoparathyroid tetany which may follow removal of a hypersecreting parathyroid tumor. It has been suggested that the body, by long endurance, has become relatively insensitive to hypersecretion of the gland and that sudden deprivation of the extra secretion results in a let-down.

In our case, shock appeared immediately after removal of the tumor and for a short period responded to epinephrine. Later, epinephrine and intravenous glucose saline had no effect but blood transfusion and administration of cortin were of immediate benefit. It may be that acute postoperative collapse is due to epinephrine deficiency and that the later and more persistent collapse is due to adrenal cortical deficiency. Transfusion has been effective in other cases and should not be delayed if epinephrine does not bring rapid improvement.

Morbid Anatomy.—Rabin[34] has given an excellent review of this and has collected interesting clinical data from thirty published cases. During fetal development the anlages of the adrenal medulla and other chromaffin tissues lie in the sympathetic ganglions which are derived from the neural crest. The lateral migration of these primitive cells (sympathogonia) is followed by differentiation along two lines, which has been plotted by Poll[32] as follows:

Sympathogonia

Sympathoblasts Ganglion cells	Pheochromoblasts

These tumors have often been called paragangliomas, a term derived from paraganglion—the embryonic origin of the entire system of ganglion cells and pheochromocytes. Since tumors of the mature sympathetic ganglion cell have been named ganglioneuromas it seems wise to name the tumors under discussion pheochromocytomas.

They usually arise within the adrenal medulla, are benign and well encapsulated and do not metastasize.

High vascularity along with a tendency to degeneration, necrosis, hemorrhage and cyst formation is the rule. Grayish white areas divide areas of congestion. The tumors vary in size from that of a pea to over a kilogram in weight, but are usually small. The size does not have any relation to the severity of symptoms.

Microscopically, the tumors consist of sheets, columns, islands or acinous formations of large polyhedral cells which contain abundant, finely granular cystoplasm and a large nucleolus. They are variable in size and shape. Fat, lipoid and glycogen are usually absent in the cytoplasm but chromate salts are often reduced to

form fine brown granules of insoluble peroxide of chromium. This chromaffinity is characteristic and is presumedly due to the strong reducing action of the epinephrine contained within the cells. Hyaline intracellular inclusions are usually seen and are similar though larger than those seen in the normal suprarenal medulla. The capsule is usually tough and fibrous and delimits the tumor from the surrounding medullary tissue and from the cortex. For further details see Rabin[34] and Belt and Powell.[4]

Pathologic Physiology.—On the evidence now available there seems little reason to doubt that these tumors form large amounts of epinephrine and that its entrance into the general circulation causes the hypertensive attacks.

Several workers have assayed tumors, and have found large quantities of epinephrine. Kalk and Buchner[16, 6] found 3 to 4 gms. pr 100 gms. of tumor; Belt and Powell[4] 2 gms. per 100 gms. of tumor.* In the case reported by Kelly et al[17] 0.13 gms. per cent of crystalline epinephrine was isolated from the tumor by Kendall. Beer et al[3] have demonstrated a pressor substance in the blood during a hypertensive crisis. Venous blood was perfused through a rabbit's ear and caused a marked pressor reaction which was abolished by ergotamine. Normal blood was without effect. Following removal of the tumor no pressor substance could be detected in the patient's blood. In the past, failure to recognize a pressor substance may have been due to inadequate method or to the rapid destruction of epinephrine in the body. It should be easier to demonstrate it in blood drawn from an artery rather than from a vein.

A number of factors may cause a flooding of epinephrine from the tumor into the blood stream. These include exercise, posture or change of posture,[3, 4, 16, 17, 27, 40, 41, 43] deep abdominal pressure or massage.[16, 43] In a number of cases[4, 11, 17, 24, 27, 40] attacks have tended to occur at definite times—often in the early hours of the morning, shortly after breakfast or associated in some way with fasting or the taking of food. This might be explained in two

*The normal adrenal gland contains about 4 to 5 mg.[38] The epinephrine content of other tumors was as follows: Fein and Carman[13] 2.2 gms. per cent; Popken[33] 0.9 gms. per cent; Rabin[34] 0.15 gms. per cent; Edward[10] 0.39 gms, per cent; Labee, Azerad and Violle[19] 0.3 gms. for entire tumor. Wells and Boman[43] 1.0 gms. %; Pincoffs[31] 1.0 gms. %; Burgess et al[7] 0.35 gms. per cent. With the exception of the case of Baker and Rienhoff[1] in which only 0.0067 gms. was found in the entire tumor, and that of Binger and Craig[5] in which more was found, all other determinations have shown large amounts of epinephrine.

ways: Epinephrine may accumulate during inactivity and later be discharged into the circulation; it may be secreted when the blood sugar is lowered by fasting or by discharge of insulin when food is taken. Both of these mechanisms exist normally and may operate in increased degree in these patients. During prolonged attacks serial determinations have shown large increases of blood sugar. In brief attacks it is difficult to sample the blood at the proper moment to demonstrate an increase. Of particular interest are the cases in which attacks resulted from anger, excitement or other emotional causes.[16, 17, 19, 30, 41, 42]

Thus attacks may occur from pressure upon the tumor, local circulatory changes, humoral causes and stimuli from the central nervous system. Sometimes no immediate cause is found. Cases in which elevation of blood pressure persists for many hours point to a steady hypersecretion of epinephrine and stimulate thought concerning the general problem of essential hypertension. Hypercholesterinemia has been noted several times and has disappeared following operation.

The spreading numbness, coldness and pallor of the digits, extremities, nose and face is due to vasoconstriction. Mayo[27] described obliteration of capillary loops in the fingernail bed. In our case measurements showed a fall of skin temperature.

The heart rate may increase or decrease during attacks. Although epinephrine increases the rate of the isolated heart by its direct action, this effect tends to be balanced in the intact animal or human by the inhibitory effect of the cardio-depressor nerves as the blood pressure rises. The balance of these two factors determines the heart rate during an attack. The cardio-inhibitor reflexes seem to be more affected by anesthesia than the direct accelerating effect of epinephrine on the heart. During operation on our case a rise of blood pressure did not cause the usual degree of slowing of the heart (Fig. 3). The basal metabolic rate is usually elevated during or shortly after an attack due to the calorigenic effect of epinephrine. No significant abnormality of the red blood corpuscles has been noted although a secondary anemia has been described in several cases. Moderate leukocytosis has been observed during attacks. In our case, an increase of leukocytes occurred due to a rise in a number of lymphocytic cells.

Coarse tremor of the head, limbs or the whole body is common.

This little known effect of epinephrine is striking and deserves investigation. We have seen it often in other patients after therapeutic doses of epinephrine. It is associated with marked hyperreflexia and often with persistent clonus at ankles and patellæ. It persists long after other evidences of epinephrine activity have disappeared. Recent studies by Schweitzer and Wright[36] throw some light on the possible mechanism of this curious effect.

SUMMARY

A case of paroxysmal hypertension, due to adrenal pheochromocytoma is described. The patient, a man of twenty-nine, had suffered attacks of increasing severity for eighteen months. Attacks lasted three to twelve minutes and were characterized by nausea, substernal distress, generalized and localized headache, tremor, pallor, numbness of extremities and were followed by exhaustion. Attacks were produced by exercise, change of posture and abdominal massage. They were intensified during fasting and relieved by nourishment. During attacks there was a great rise of blood pressure, slowing of heart rate, disappearance of radial pulse, drop in skin temperature, lymphocytic increase in blood stream and glycosuria. In the intervals between attacks the blood pressure was normal and there was no cardiovasular abnormality. Plain roentgenograms, intravenous pyelography and massage over the adrenal glands failed to demonstrate the tumor. Exploration of the left adrenal region revealed no tumor. The opposite side was explored and an encapsulated pheochromocytoma the size of a golf ball (24 gms.) was removed from the adrenal medulla. An extract of it contained a large amount of epinephrine (0.38 gms. per 100 gms. tumor). No further attacks occurred following operation and eleven months later the patient reports himself entirely well.

Data are recorded from twenty cases which have come to operation. Five patients died and fifteen were completely relieved. Evidence indicates that the paroxysms of hypertension are due to intermittent hypersecretion of epinephrine by the adrenal chromaffin tumor.

BIBLIOGRAPHY

1. Baker, B. M., Jr., and Rienhoff, W. F., Jr.: To be published. See Howard and Barker[35] for summary.

2. Bailliart, P.: The Retinal Circulation. Chicago: The Professional Press Inc., 1928.
3. Beer, E., King, F. H., and Prinzmetal, M.: Pheochromocytoma with demonstration of pressor (adrenalin) substance in the blood preoperatively during hypertensive crises. Ann. Surg., 106:85, 1937.
4. Belt, A. E., and Powell, T. O.: Clinical manifestations of the chromaffin cell tumors arising from the suprarental medulla. Surg., Gyn. and Obst., 59:9, 1934.
5. Binger, M. W., and Craig, W. McK.: An atypical case of hypertension with a tumor of the adrenal gland. Proc. Staff Meet. Mayo Clinic, 13:17, 1938.
6. Büchner, F.: Spezifische Tumoren des Nebennierenmarks mit Hypertonie. Klin. Wchnschr., 13:617, 1934.
7. Burgess, A. M., Waterman, G. W., and Cutts, F. B.: Adrenal sympathetic syndrome with unusual variations in cardiac rhythm. Arch. Int. Med., 58:433, 1936.
8. Coller, F. A., Field, H., and Durant, T. M.: Chromaffin cell tumor causing paroxysmal hypertension relieved by operation. Arch. Surg., 28:1136, 1934.
9. Donzelot, E.: Les hypertensions paroxystique. Bull. et mem. de l. soc. med. des hop. de Paris, 2:1510, 1934.
10. Edward, D. G.: Pheochromocytoma and hypertension. Jour. Path. and Bacter., 43:391, 1937.
11. Evans, V. L.: Suprarenal tumor with paroxysmal hypertension. Jour Lab. and Clin. Med., 22:1117, 1937.
12. Fein, M. J., and Carman, F. F.: Medullary carcinoma of suprarenal gland (pheochromocytoma). Amer. Jour. Cancer, 29:301, 1937.
13. Folin, O., Cannon, W. B., and Denis, W.: A new colorimetric method for the determination of epinephrine. Jour. Biol. Chem., 13:477, 1923.
14. Gärtner, W.: Das klinische Bild, insbesondere die Kreislaufstörungen, bei Paragangliom der Nebenniere. Ztschr. f. Kreislaufforschung, 28:82, 1936.
15. Howard, J. E., and Barker, W. H.: Paroxysmal hypertension and other clinical manifestations associated with benign chromaffin cell tumors (pheochromocytoma). Bull. Johns Hop. Hosp., 61:371, 1937.
16. Kalk, H.: Paroxysmale hypertension. Klin. Wchnschr., 13:613, 1934.
17. Kelly, H. M., Piper, M. C., Wilder, R. M., and Walters, W.: Case of paroxysmal hypertension with paraganglioma of the right suprarenal gland. Proc. Staff Meet. Mayo Clin., 11:65, 1936.
18. Kremer, D. N.: Medullary tumor of the adrenal glands with hypertension and juvenile arteriosclerosis. Arch. Int. Med., 57:999, 1936.
19. Labbé, M., Azerad, E., et Violle, P. L.: Adenome medullaire surrénale et hypertension paroxystique. Bull. et mém. de l. soc. méd des hôp. de Paris, 53:952, 1929.
20. Labbé, M., et Nepveux, F.: Un cas d'hypertension paroxystique d'origine surrénale. Bull. et mém. de l. soc. méd. des hôp. de Paris, 1:337, 1934.
21. Labbé, M., Tinel, J., et Doumer: Crises solaires et hypertension paroxystique en rapport avec une tumeur surrénale. Bull. et mém. de l. soc. méd. des hôp. de Paris, 46:982, 1922.
22. Landau, A., Paskiewicz, L., Slawinski, Zd., et Steffen, E., Jr., Hypertension paroxystique grave consécutive à une tumeur de la surrénale (paragangliome). Rev. belge. de sc. Méd., 8:330, 1936.
23. Lazarus, J. A., and Eisenberg, A. A.: Tumors of adrenal gland. Report of two cases of paraganglioma of adrenal gland. Jour. Urol., 27:1, 1932.
24. Leriche, R.: Hypertension paroxystique. Ablation d'un paragangliome extrasurrénalien. Guerison. Lyon Chirurgie, 31:355, 1934.
25. McKenna, C. M., and Hines, L. E.: Paraganglioma of the suprarenal gland. Jour. Urol., 34:93, 1935.

26. MASSON, P., and MARTIN, J. F.: Paragangliome surrénale, étude d'un cas humain des tumeurs malignes de la médullo-surrénale. Bull. A. franc. p. l'étude de Cancer, 12:135, 1923.
27. MAYO, C. H.: Paroxysmal hypertension with tumor of retroperitoneal nerve. Jour. A.M.A., 89:1047, 1927.
28. OPPENHEIMER, B. S., and FISHBERG, A. M.: The association of hypertension with suprarenal tumors. Arch. Int. Med., 34:631, 1924.
29. PENFIELD, W.: Diencephalic autonomic epilepsy. Arch. Neur. and Psych., 22:358, 1929.
30. PINCOFFS, M. C.: A case of paroxysmal hypertension associated with suprarenal tumor. Trans. Assoc. Amer. Physicians, 44:295, 1929.
31. PINCOFFS, M. C.: To be published. See Howard and Barker[18] for summary.
32. POLL, H.: Die vergleischende Entwicklung der Nebennierensysteme. Hertwig. Handbuch der Entwicklungsgeschicte der Wirbeltiere, Jena; Gustav Fischer, 1906, v. 3, p. 442.
33. POPKEN, C.: Über chromaffine Tumoren. Beitr. path. Anat., 97:337, 1936.
34. RABIN, C. B.: Chromaffin cell tumor of the suprarenal medulla (pheochromocytoma). Arch. Path., 7:228, 1929.
35. ROWNTREE, L. G., and BALL, R. G.: Diseases of the suprarenal glands. Endocrinology, 17:263, 1933.
36. SCHWEITZER, A., and WRIGHT, S.: The action of adrenalin on the knee jerk. Jour. Physiol., 88:476, 1937.
37. SHIPLEY, A. M.: Paroxysmal hypertension associated with tumor of the suprarenal. Ann. Surg., 90:742, 1929.
38. SOLLMAN, T.: A Manual of Pharmacology. Philadelphia & London: 1934, W. B. Saunders, p. 453, 4th ed.
39. SUERMONDT, W. F.: Paroxysmale Blutdruckerhöhung, geheilt durch Extirpation einer Nebennierengeschwulst. Zentrlbl. f. chir., 61:70, 1934.
40. VAN GOIDSENHOVEN, F., and APPELMAS, R.: Contribution à l'étude clinique et thérapeutique de L'hypertension paroxystique d'origine médullo-surrénalienne. Bull. Acad. Roy de méd. de Belgique, 14:672, 1934.
41. VOLHARD, F.: Nieren und ableitende Harnwegen. Handbuch der interne Medizin 11 Teil, p. 1742, 1931.
42. WELLS, A. H., and BOMAN, P. G.: The clinical and pathologic identity of pheochromocytoma. Jour. A.M.A., 109:1176, 1937.
43. PORTER, M. F., and PORTER, M. F., Jr.: Report of a case of paroxysmal hypertension cured by removal of an adrenal tumor. Surg., Gyn. and Obst., 50:160, 1930.

DISCUSSION

DR. ELDRIDGE L. ELIASON (Philadelphia, Pa.): I would like to thank Dr. Alexander Randall for this privilege accorded by him and by you.

I haven't had much experience in this interesting condition. In fact, we are infants in the study of it, probably in swaddling clothes, so to speak. We have had only five or six operative cases, four of which I think might be of interest to you. They were of extreme interest to us from every standpoint, particularly because we knew nothing about what we were doing until after we studied them, and then we couldn't understand in all respects just what happened to the patients.

The first patient fits in with one group of Dr. Cahill's, a young lady who had the prettiest masculine build you would see on any track athlete, a full beard, amenorrhea since birth, had only menstruated once. She was sixteen years of age when Dr. Palmer and Dr. Lukins determined a right adrenal tumor. We removed it and the young lady recovered. In three months she started to menstruate and has menstruated regularly since. She developed a feminine build, and now she shaves only once every second day when she used to shave twice, and the hair on her trunk and her legs has practically disappeared.

The interesting thing about this woman, to my mind, from the photographic standpoint was the loss of her beautiful masculine leg and the replacing of it by an ordinary feminine leg (laughter), not nearly so beautiful.

The second case was a child of five, with a precocious development and a large tumor in the left subcostal region, the region of the left kidney. This case was in the Philadelphia General Hospital, and the genito-urinary surgeons objected to my having scheduled this case for a nephrectomy. Fortunately, we hadn't completely studied the case and it was not put on the operating schedule. We postponed it and asked the genito-urinary men if they would study the case and take it over if they wished to. They took it over as an adrenal tumor, operated and found a normal kidney and adrenal on the right side. They transferred the patient back to us, and through a transperitoneal approach we re-

moved a tumor from the region of the hilus of the left kidney. This tumor was about the size of a tennis ball. At the post-mortem examination, this child was found to have a normal kidney and adrenal on each side, and the pathologists reported this tumor as an intrarenal gland, cortical in nature.

The third case of interest was that of an angioblastoma. This patient is of interest purely from the diagnostic standpoint. She was a colored woman, aged thirty-six, admitted to the hospital with what looked like acute cholecystitis, characterized by upper abdominal pain, nausea, vomiting, with a history of a few days duration. She had also only 1,200,000 red blood cells and 26 per cent hemoglobin. We thought of intra-abdominal hemorrhage, but this was ruled out. We watched her a few days, and I operated upon her for acute cholecystitis, She did not have it, but she did have a black tumor mass behind her peritoneum. This was opened and a large, thick, black clot of about ten or twelve days' duration was exposed. We did not know the origin of the hemorrhage. Twenty-four days later she died. At post-mortem she was found to have widespread, extensive metastasis of angioblastoma type, in mesentery, diaphragm, kidneys, lungs, heart and pericardium, whereas twenty-four days previously there wasn't a single evidence of metastasis in the abdomen.

The fourth case, in brief, unfortunately gave us the same experience that Dr. Cahill mentioned. This woman had the right adrenal removed. She was hypertensive, of the obese type, and although the operation went very nicely, she died on the fifth day with a temperature of 106 to 107, despite the fact that her blood pressure was sustained at almost the normal rate. At postmortem examination, it was found that she had no demonstrable adrenal on the left side, and although we had left practically all of the adrenal on the right, removing a tumor of about three and a half centimeters, we thought we left enough adrenal to sustain life. Apparently she died of what we termed at that time "adrenal shock."

Since these cases we have had quite a few hirsutism cases that have presented themselves as a result of an unfortunate experience when one of these cases was given publicity in the public press. Subsequently, a lot of hairy women began to write in to

the hospital and our endocrine clinic began to get busy and needed more than one razor to keep up with the crowd.

That is our interesting experience in this particular lesion, gentlemen.

PRESIDENT RANDALL: Dr. Eliason, did you want to inquire in regard to diagnosis?

DR. ELIASON: I would like to. When I sat down I acknowledged that we knew nothing about the condition, but failed to state that we had a catastrophe that I do think should be a matter of record in the question of air injection for diagnostic purposes.

This woman, one of the obese type, had an air injection of some 250 c.c. on her left side, and during the injection of the right side, the needle met blood. It was withdrawn, the blood removed and a needle inserted again, air suction applied to the plunger, no blood was noted, and air was then injected in the amount of 200 c.c. The patient suddenly collapsed, got markedly dyspneic, cyanotic, and the appearance of the skin looked very much like subcutaneous suggilations, particularly on the trunk and the hands. The pulse dropped to 40, and was very irregular. In about an hour the patient succumbed.

This was the first catastrophe we had in the University Hospital. I don't suppose we have done more than maybe forty or forty-five air injections all told. Although air injection is a simple procedure, something serious can happen, and this is one case at least that resulted disastrously. I forgot to speak about this when I was on my feet before. I do think we ought to recognize that it isn't, at least in our hands, a simple diagnostic procedure without danger.

DR. WILLIAM E. LOWER (Cleveland, Ohio): Some years ago, there was referred to our department at the hospital a child three and one-half years of age who had been menstruating regularly. She had well developed breasts and suprapubic hair, and the question of possible adrenal tumor was considered. That was before the days that we knew much about adrenal tumors or air injections for diagnosis. I explored one side and found a large suprarenal gland but no tumor apparently, so I exposed the other side and found a similar condition. Not knowing exactly what to do

but feeling that these glands were larger than normal, I resected both suprarenals. The child stopped menstruating; and did not menstruate again until she was thirteen years of age Since then she has menstruated regularly and is about a normal child. Just what the condition was that disturbed this endocrine balance I don't know, but all we did was to resect part of each suprarenal gland.

Dr. William C. Quinby (Boston, Mass.): Permit me to congratulate Dr. MacKenzie and Dr. Cahill, as well as our guest, Dr. Eliason, for their stimulating presentation of various aspects of disease caused by disturbances of the adrenal gland. The clinical phenomena caused by such may be quite varied in so far as they relate to disturbances of the cortex of the gland. The phenomena seen are frequently related to an increase in those physical characteristics significant of the male. You will remember a patient whose history I reported before this society, a boy whose career had been one of precocious development until the age of eleven, at which time he died of an inoperable malignant growth of the cortex of the adrenal gland.

Instances such as Dr. Cahill has related in women are becoming increasingly frequent in our clinic, largely because of the fact that the condition is productive of a marked increase in bodily hair, especially that of the face. Needless to say, this is exceedingly disturbing to women and they are eager for advice as regards its relief.

Dr. Cahill's communication illustrates brilliantly adrenal conditions which may be found under such circumstances. I wish to point out, however, that in such unfortunate individuals we must evaluate, as far as we can do so, the activity of all the endocrine glands as well as that of the adrenal. For instance, we know that in the acromegalic patient there is an enlargement of the adrenal. Furthermore, in those instances of pituitary adenoma demonstrated by Cushing, one sees almost the same picture as is seen in the patients described by Dr. Cahill, except that possibly there may be less overgrowth of hair and a more definite accompaniment of increasing fat of the abdomen with its striæ, leaving the legs and arms thin. There is no doubt in my mind that from such work as has been reported we are on the way toward a much more detailed understanding of these continuously perplexing cases.

As concerns Dr. MacKenzie's communication, I assume that the tumor took origin in the medullary portion of the adrenal; namely, in the portion which in lower animals is called the "intrarenal body," and is of nervous origin.

DR. QUINBY: I reported three years ago the same happening which Dr. Eliason has just mentioned. We also had a catastrophe from diagnostic air injection.

DR. CAHILL: Three points are of major interest, the hormonal excretions up to the present, the findings necessary for diagnosis of tumor, and the immediate operative prognosis in hormonal tumors.

The adrenal medullary hormone, epinephrine, was early identified and isolated, largely because of its concentration in the gland. Only recently have a number of substances been isolated from the cortex and they apparently are in the process of identification. Among the first was the male sex hormone, androsterone, and in cases of androtrophic symptoms, either from tumor or otherwise, it is excreted in the urine in relatively large amounts that apparently are an index of the degree of masculinization. As yet the substances responsible for the other metabolic changes have not been identified.

In order to establish the diagnosis or to rule out a tumor, we have used air injection radiographs in approximately 140 cases. Filtered air introduced below the twelfth rib, near the edge of the erector spinæ diffusing under the tranversalis fascia, outlines the outside of the renal fatty capsule and enables the adrenal to be visualized by x-ray. After injection the air is diffused by exercise or by manual manipulation. Radiographs taken twenty-four hours or more afterwards may clearly show the fascial planes. In the proceeding, the risk of air embolus is small, if care is taken to avoid penetration of a blood vessel. This can be done by aspiration after each movement of the needle. If blood was obtained by us no air injection was made, but the procedure was postponed and injection made again several days later. None of our adrenal air injections had any complications. I know of two fatalities, one from air embolus where a large infiltrating retroperitoneal tumor was injected and the second from a coronary occlusion at the time of the procedure. With the exception of

exploration, this method up to the present appears to be the best to estimate the anatomy of the adrenal glands.

An adrenal tumor causing mainly sex changes apparently does not upset the opposing adrenal, if present, and operative removal of the tumor is without much disturbance. When other metabolic changes occur, operative removal is hazardous, although there is hope that experimental data may suggest preoperative therapy.

When the described syndromes are present without tumor, actual proof of the causation is as yet undetermined, although the adrenal is known to play some important part in the changes.

DR. MACKENZIE: We have done quite a number of airgrams (perhaps too many) with only one casualty. We have used the filtered air. We have used carbon dioxide, but filtered air is the favorite. We have often seen the injection very much as Dr. Cahill says, and we have often seen the best airgrams seven days after injection; perhaps you have the same experience. Often the one that comes quite late will either partially contradict or confirm the ones that were more doubtful in the early stage.

Coming back to one of our medullary tumors: Those medullary tumors in the literature are found all the way down to the gonad region just as the cortical portion is, and several tumors have been found quite below the kidney. But in the second case, a little girl of six was a delicate little creature and supposed to be somewhat temperamental and a neurologic patient. After building her up quite carefully, it was decided to do an airgram, but as previously, with a hypodermic of morphia of one-eighth, the puncture of the needle caused her blood pressure to go up and later she went into profound shock. Nobody wanted to do an airgram, so the whole family gathered around, including the medical men, and the needle was injected in the proper place. It went in very slowly, and by the time she had about a fifth of the ordinary dose she said she felt some fullness in the side. The needle was withdrawn and she was dead in fifteen minutes.

A complete autopsy was done at once. No vessel was found where the needle had entered.

MULTIPLE PRIMARY CANCERS

HERMAN L. KRETSCHMER, M.D.

Chicago, Illinois

The subject of multiple primary malignant neoplasms is of great interest to the surgeon for the following reasons: first, he is faced with the surgical management of two primary malignant tumors instead of one; second, it may mean one or two major surgical procedures, depending on the location of the tumors; in the third place, the surgeon is faced with the problem of obtaining a cure of two or more malignant tumors in the same patient. The fourth problem that presents itself to the surgeon is the question of pathology: he must determine by careful histological study the exact nature of the tumors, so that he can present evidence showing that he is actually dealing with two different independent malignant tumors.

Not only is this subject of great interest to the surgeon but it is equally interesting to the pathologist and to all students of the cancer problem.

Multiple primary malignant tumors occurring in the same patient may be classified in two groups: in the first group are cases in which the tumors are present when the patient comes under observation. In the second group are cases in which multiple malignant tumors occur in succession, that is, the patient has been cured of one malignant tumor and subsequently has developed a second or even a third tumor. In other words, in the first group the patient has multiple malignant tumors present at one and the same time, and in the second group the patient has multiple tumors which are not present at the same time but develop in succession.

This paper is based on my personal experience of five cases. A case of multiple primary malignancy, previously reported by Heckel and myself, in which a male had a carcinoma of the urinary bladder and a primary carcinoma of the breast is not included. In four of them the tumors were present at one and the same time, and in the fifth case the patient belonged to the second classification as mentioned above. As far as the genito-urinary tract is concerned, one may state that the occurrence of multiple primary

tumors in the genito-urinary tract is uncommon in comparison with the frequency of occurrence in other parts of the body, *e.g.*, the gastro-intestinal tract; this is evidenced by a review of a large series of cases that have been reported.

Thus, Hurt and Broder, in their publication, reported a series of seventy-one cases, in which there were only three cases where one or both of the tumors occurred in the urinary tract.

There seems to be an increased interest in this subject, both by the surgeon and pathologist, as evidenced by the rather sharp increase in the number of publications dealing with this subject.

Before discussing this subject in detail I wish to present the following five cases:

Case 1.—(a) *Epidermoid Carcinoma of the Urinary Bladder;* (b) *Adenocarcinoma of the Prostate Gland With Extension Into the Wall of the Seminal Vesicles.*

F. S., male, aged eighty-one years, was admitted to the Presbyterian Hospital, December 5, 1937.

Complaints on admission were hematuria, nocturia, frequency, nausea, vomiting, great weakness, and loss of weight.

The patient stated that he was obliged to arise once a night for a great many years. Three months ago he had a very severe attack of hematuria. With his first attack he passed large blood clots. As a rule the bleeding persisted for two or three days. Subsequently, he had ten or twelve attacks of hematuria.

At this time the nocturia rapidly increased; whereas heretofore he was obliged to arise only once at night, he now was obliged to get up from four to six times. Since the onset of the hematuria he had no appetite and had lost 35 pounds in weight. He complained of a marked slowing of the urinary stream and great hesitation, so that he was obliged to wait for as much as one or two minutes before he could get the stream started. For the past six weeks, he stated, he has had swelling of the ankles and legs.

Physical Examination.—The patient was an exceedingly pale, weak, and very poorly nourished white male. There were several small pedunculated masses, the size of peas, in the roof of the mouth at the junction of the hard and soft palate. Examinations of the head, and neck showed no abnormalities. There was a bilateral inguinal hernia. The external genitalia were negative except for a left-sided epididymitis.

Rectal examination revealed external hemorrhoids. Sphincter tone was good. Prostate was enlarged (3 to 4 plus); the surface very irregular and nodular, and the consistency stony hard. In the right lobe there was an area very hard, nodular, and raised above the surface of

the gland. Both seminal vesicles were hard and thickened and rolled under the finger.

There was moderate edema of both ankles.

Residual urine: 350 c.c.

Urine: Albumin, white blood cells, and occasional red blood cells. Sterile on culture.

Blood: 2,900,000 red blood cells; 10,000 white blood cells; hemoglobin, 52 per cent. Blood chemistry: urea nitrogen, 133.4; creatinine, 6.0; non-protein nitrogen, 148.2. Blood pressure: systolic, 155; diastolic, 80.

The electrocardiogram was within normal limits.

Roentgen-ray examination revealed no stone; no evidence of bone metastases. There was some lipping between the margins of the lumbar vertebræ.

Intravenous pyelograms showed no visualization of media from either kidney.

A cystogram showed a small contracted bladder with multiple cellules.

Cystoscopic examination was made on December 7, 1937. The resectoscope was introduced with some difficulty because of an obstruction in the prostatic urethra. The bladder was filled with very large blood clots and it was necessary to remove them with the Bigelow evacuator. Many necrotic masses of tumor tissue were removed at this time. Examination of the bladder with the cystoscopic telescope of the resectoscope showed a very large necrotic tumor that was more or less papillary in appearance. Because of the size of the tumor and the bleeding it was difficult to determine the exact point of origin of the tumor. Examination of the prostatic urethra showed irregularities and several bleeding points. All the bleeding points in the prostatic urethra and all bleeding points that could be located in the bladder tumor were fulgurated.

Histologic examination of the pieces of bladder tumor that were obtained from the wash water showed epidermoid carcinoma of the urinary bladder (Fig. 1).

Repeated chemical studies of the blood:

Date	Urea N.	Creat.	N.P.N.
Dec. 6	133.4	6.0	148.2
9	112.3	6.0	285.7
10	89.7	5.2	105.3
11	92.6	5.0	108.7
13	91.0	5.9	113.0
15	82.6	5.5	98.5
17	76.9	4.4	87.7
20	84.9	4.3	104.1
24	95.2	5.6	102.0

During the patient's stay in the hospital he was given several blood transfusions, intravenous administrations of glucose, and alkaline diu-

retics. Urethral catheter drainage was instituted. His temperature varied from 98.3 to 102 degrees.

Because of the severe bleeding repeated fulgurations were carried out. The question of the advisability of performing a suprapubic cystostomy was discussed at various times, but was thought inadvisable because of his poor condition.

The patient died on December 26, 1937.

The *autopsy* was performed by Dr. Carl Apfelbach and the anatomic diagnosis was as follows: carcinoma of the urinary bladder; carcinoma of the prostate; chronic prostatitis and periprostatitis; bilateral hydroureter and bilateral cystoureteropyelitis; bilateral pyelonephritis; acute bronchopneumonia; bilateral acute fibrinous pleuritis; generalized anasarca; generalized anemia; retrogressive changes in the liver and pancreas; atrophy of the spleen; healed bilateral apical tuberculosis with adhesions; diverticulosis coli; generalized arteriosclerosis; benign nephrosclerosis; marked visceroptosis; disseminated long-since healed scars in the peritoneum; hypertrophy of the left ventricle.

Gross Description.—The posterior wall and part of the lateral wall of the bladder were occupied by a fungating mass of yellowish tissue. The prostatic urethra was of normal form. The prostate gland was enlarged and very hard. On the cut surface, islands of bright yellow tissue with the appearance of normal hypertrophic prostatic lobules were seen. Between them there was unusually dense white fibrous tissue. An unusual amount of hard white tissue extended posteriorly and involved the lower portions of the seminal vesicles.

The histologic examination of the urinary bladder showed epidermoid carcinoma. Sections made from the prostate gland showed the presence of adenocarcinoma of the prostate (Fig. 2).

Case 2.—(a) *Carcinoma of the Urinary Bladder;* (b) *Hypernephroma (Right Kidney).*

R. W. B., male, aged sixty-one years, was admitted to the Presbyterian Hospital, December 25, 1936.

The patient stated that seven years ago he had a suprapubic cystostomy and surgical diathermy for a tumor of the bladder. In January, 1936, he had a return of his old symptoms and fulguration was done through the cystoscope (elsewhere).

In August, 1936, he had constant burning pain in the perineum, which would often be accompanied by urgency. This was associated with great frequency of urination, so that he usually would void every ten minutes during the day and three or four times at night. The frequency gradually became less as did also the burning until he voided only once or twice an hour. After two weeks he noticed that the urine was bloody. At the time of admission the urine was still bloody, the burning was not severe, and the frequency occurred every one or two hours during the day and three times at night.

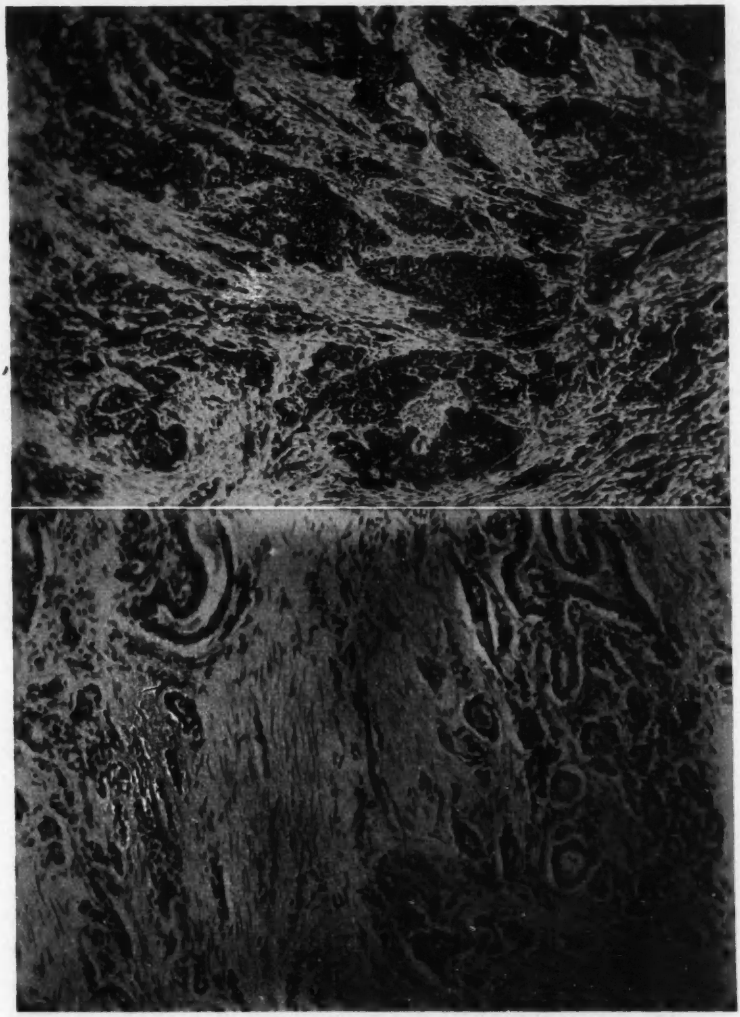


Fig. 1. (*above*) Case 1. Carcinoma of bladder. Note infiltration of muscle layers by epidermoid carcinoma.

Fig. 2. (*below*) Case 1. Adenocarcinoma of prostate.

Physical Examination.—The patient was a small, well-nourished, white male, apparently in good health. The right eye was absent. Examination of the head, neck, chest, and lungs revealed no abnormalities. The heart had a slight systolic murmur at the apex. Abdomen was normal. External genitalia were normal.

Rectal examination revealed a moderate enlargement of the prostate (one plus); it was soft, smooth, and elastic, the right lobe slightly larger than the left, and tender. The seminal vesicles were soft. There were no signs of carcinoma.

There was no residual urine.

Urine: Albumin, blood, and pus. Cultures were sterile and no tubercle bacilli were found.

Blood: 3,880,000 red blood cells, 8,200 white blood cells, hemoglobin 72 per cent. Blood pressure systolic, 155; diastolic, 80.

Roentgen-ray examination showed the kidney outlines to be of normal size and position. There were no areas of increased density suggesting stones. There was slight lipping from the margins of the lumbar vertebræ on an arthritic basis, but no evidence of bone metastases.

Intravenous pyelograms: Both right and left pyelograms were normal.

A cystogram showed a filling defect on the right side of the bladder.

Cystoscopic examination on December 26, 1936, revealed multiple papillary tumors which varied in size from a lima bean to the size of a plum. The largest tumor was on the left lateral wall, and the surface was necrotic. In the dome were two necrotic tumors about the size of unshelled almonds. On the right lateral wall were several papillary tumors. On the base of the bladder were four papillomata, varying in size from a pea to an unshelled hazel nut. In the region of this group were several groups of smaller papillomata which protruded a small distance above the mucous membrane. Because of the presence of these necrotic tumors and a filling defect in the cystogram, a diagnosis of carcinoma was made. There was slight lateral lobe hypertropy of the prostate with a median commissure.

On December 28, 1936, under sacral anesthesia, the tumors were resected and fulgurated with a McCarthy resectoscope, and at this time a resection of the prostate was done.

Histologic examination of the pieces removed from the bladder indicated papillary epidermoid carcinoma (Fig. 3); of the section removed from the prostate, benign adenoma.

Following the operation the patient developed acute pyelitis. He was discharged from the hospital on January 11, 1937.

Second admission to the hospital was on February 15, 1937, because of bladder spasms and the passage of large blood clots. Bladder spasms were severe, accompanied by a great deal of pain. The tumors were again fulgurated.

After his discharge from the hospital in February, the patient was

fairly comfortable for about four weeks, at which time his symptoms returned. He experienced pain on urination, great frequency, both day and night, and imperative urination; some pain and aching in the rectum. During this period he lost 10 pounds in weight.

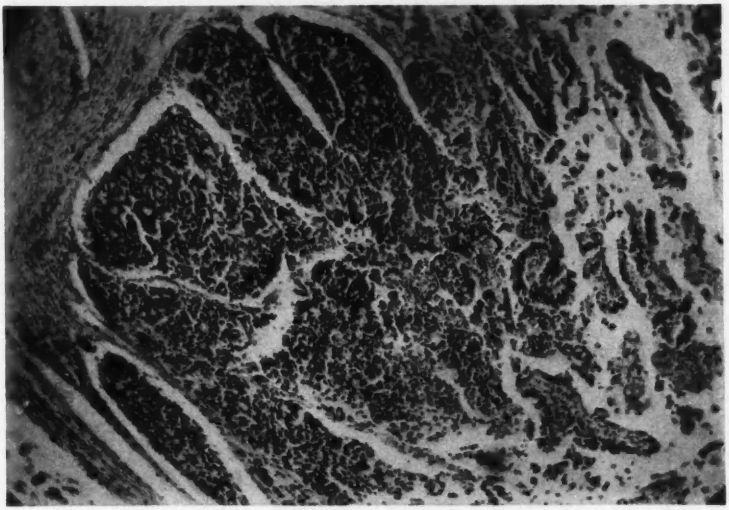


Fig. 3. Case 2. Epidermoid carcinoma of bladder.

There was no change in the physical examination. Rectal examination: slight tenderness of the prostate. Examination of the urine: albumin, many white and red blood cells. Cultures: B. Coli communis. Blood examination: 3,880,000 red blood cells, 10,400 white blood cells, and hemoglobin 68 per cent. Blood chemistry: urea nitrogen, 8.7; creatinine, 1.3; non-protein nitrogen, 28.6.

Because of recurring attacks of bleeding, great frequency of urination and the presence of severe pain that could not be controlled with morphine, the patient was advised to have a suprapubic cystostomy and surgical diathermy of his tumors.

A preliminary blood transfusion was given before the operation.

A suprapubic cystostomy and surgical diathermy were done on April 9, 1937; 7,200 milligram hours of radium were given.

Sections of the tumor removed at this time showed, on histologic examination, papillary carcinoma of the urinary bladder.

Following his discharge from the hospital he gained in weight and

had a comfortable summer. In the autumn pain returned, gradually increasing in severity, and severe bladder spasms developed. The desirability of total cystectomy with transplantation of the ureters into

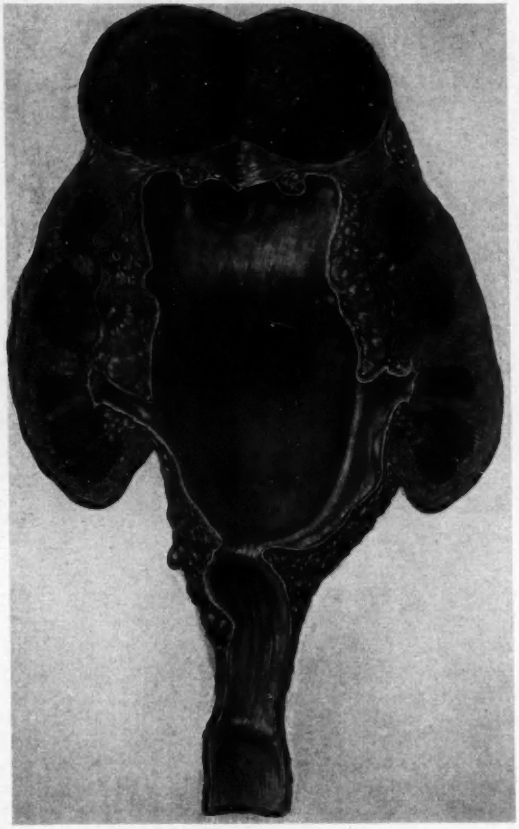


Fig. 4. Case 2. Hypernephroma in upper pole of kidney.

the skin was suggested. The patient decided to re-enter the hospital and be operated on.

On December 13, 1937, a complete cystectomy, with removal of the prostate and transplantation of the ureters into the skin, was done.

For one week following the operation, the patient ran a smooth and

uneventful convalescence. On December 20, there was evisceration and this was repaired. At the time this was done, evidence of peritonitis was present. For one or two days he was comfortable and then developed generalized abdominal tenderness, fever, and pain. This was fur-

Fig. 5. Case 2. Hypernephroma.

ther complicated by the development of pulmonary congestion which was a progressive thing and finally the lungs began to be filled with moisture so that coarse moist râles were heard throughout the lung fields. A diagnosis of bronchopneumonia was made. The patient died on December 25, 1937, death being due to generalized peritonitis and acute bronchopneumonia.

The autopsy was performed by Dr. Carl Apfelbach. The diagnosis was: carcinoma of the urinary bladder; hypernephroma of the right kidney (Fig. 4); bilateral hydroureter; bilateral pyelitis; bilateral pyelonephritis; multiple scars in both kidneys; tortuosity of right ureter with ureteritis in distal portion; pyogenic abscesses of base of right kidney; generalized peritonitis with adhesions; thickened white gall bladder wall with one large cholesterol stone; generalized arteriosclerosis; pulmonary edema with gross fluid in pleural cavity; aspiration bronchopneumonia; old healed pleuritis of left apex with adhesions; thickening of pleura of right apex; enlarged tracheobronchial and hilar lymph nodes; acute dilatation of stomach; paralytic ileus; old healed

scar in right myocardium; generalized sclerosis of coronary vessels; cloudy swelling of liver and pancreas; old healed collar incision; unhealed subumbilical incision; healing stab incisions in both lower quadrants; right incision infected.

Histologic examination of the small remnants of tumor in the bladder indicated papillary carcinoma.

Examination of specimens removed from the kidney tumor showed hypernephroma (Fig. 5).

Case 3.—(a) *Carcinoma of Prostate;* (b) *Papillary Epidermoid Carcinoma of the Urinary Bladder.*

E. M., male, aged seventy-nine years, was admitted to the Presbyterian Hospital, November 21, 1937, referred by Dr. F. W. Allin.

The complaints on admission were frequency, nocturia, dysuria, hematuria, and difficulty in starting the urinary stream. The patient stated that during the previous year he had suffered from difficulty in starting his stream. He also suffered from frequency of urination about every two to three hours throughout the day. Burning was associated with urination and on several occasions some gross blood was passed. There were chills and fever.

Physical Examination: The patient was a well-nourished male, apparently not ill. Examination of the head, neck, chest, heart, abdomen, and external genitalia revealed no abnormalities.

Rectal examination showed the prostate moderately enlarged (2 plus). The surface was smooth, not nodular, borders sharply defined; consistency markedly increased. Although the prostate was not nodular but was very hard, a tentative diagnosis of carcinoma was made.

Residual urine: Six ounces.

Urine: Pus, red blood cells, and a trace of albumin. No organisms on culture or smears.

Blood: 4,500,000 red blood cells; 7,000 white blood cells; hemoglobin 85 per cent. Blood chemistry examination: urea nitrogen, 21.4; creatinine, 1.5; non-protein nitrogen, 40.2; urea chloride, 24. Blood pressure: systolic, 150; diastolic, 90.

Phenolsulphonephthalein test showed an output of 70 per cent in one and one-half hours and the time of appearance was eleven minutes.

Electrocardiogram revealed coronary disease, marked left axis deviation, and myocardial damage.

Roentgen-ray examination showed the kidney outlines to be normal in size and position. There were no areas of increased density suggesting stones. There was marked lipping from the margins of the lumbar vertebræ on an arthritic basis, but no evidence of bone metastases.

Examination with the cystoscope and the resectoscope was done on November 23, 1937, under sacral anesthesia. A large papillary

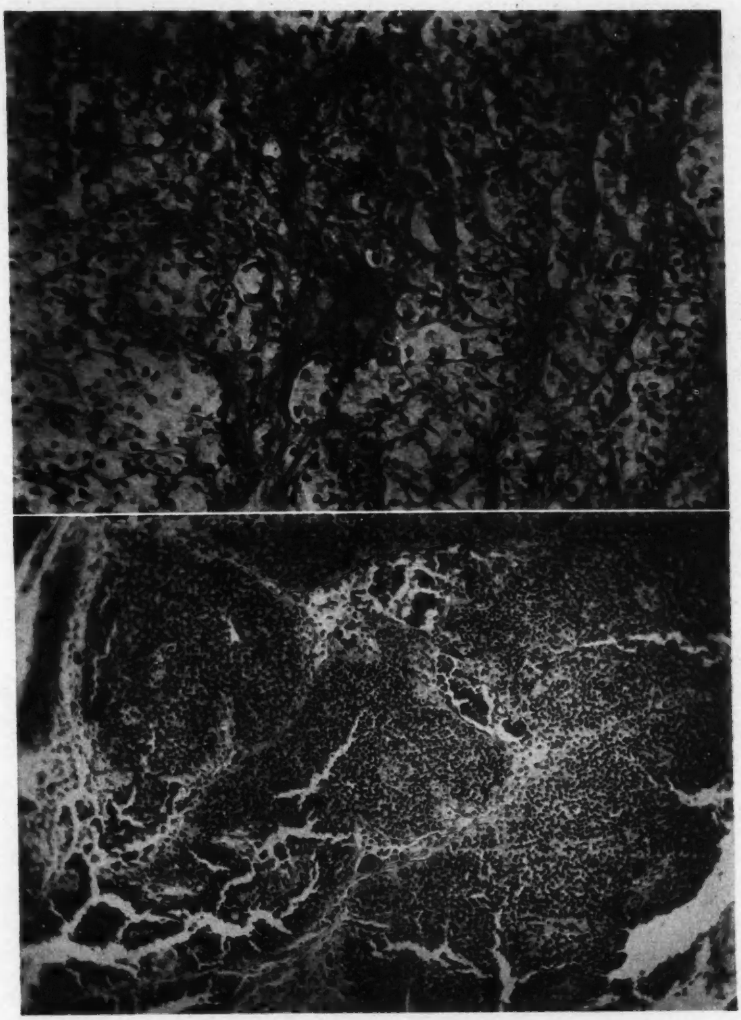


Fig. 6. (*above*) Case 2. Papillary epidermoid carcinoma of prostate.
Fig. 7. (*below*) Case 2. Papillary epidermoid carcinoma of bladder.

tumor was seen on the left lateral wall of the bladder above the left ureteral orifice. Prostatic tissue completely surrounded the internal ureteral orifice, irregular at the base. Pieces of the large papillary tumor were removed with the loop for histologic study and the tumor was fulgurated. A resection of the prostate was carried out.

Pathologic diagnosis of the tissue removed from the prostrate was adenocarcinoma; and of the tissue removed from the bladder, papillary epidermoid carcinoma.

After an uneventful convalescence the patient was discharged December 3, 1937.

Deep x-ray therapy was advised and carried out after his discharge from the hospital.

He was readmitted March 25, 1938, because of frequent urination both day and night, severe burning and pain on urination, constant suprapubic and perineal pain, and blood in the urine. Because of the great severity of symptoms a permanent suprapubic cystostomy was done. Papillary tumors on both lateral walls were fulgurated and 100 milligrams of radium were inserted into the base of the bladder. A total of 3,000 milligram hours of radium was given. Following the cystostomy, the patient's temperature returned to normal and remained so. Following the operation a diarrhea developed which was very severe, so that he had a bowel movement every fifteen to twenty minutes. This was controlled by opiates and bismuth powders. A gastro-intestinal study, including proctoscopic examination, stool examinations, and colon fluoroscopy, showed no possibility of another neoplasm. The stools showed considerable pus, and the rectal and sigmoid were markedly edematous, red, and congested. At the present time the patient's bowel condition is much improved. He continues to have slight pains at the head of the penis at times.

Case 4.—(a) *Carcinoma of the Prostate;* (b) *Epithelioma of the Ear.*

C. C., male, aged eighty-two years, was admitted to the Presbyterian Hospital, October 29, 1931, on the service of Dr. Ralph C. Brown.

The complaints on admission were as follows: For many years the patient has had a skin cancer on the left ear. He has had a course of radium treatments with some improvement in the cancer.

For the past five years he has had frequency of urination, both day and night, that has grown progressively worse. During this time there was a gradual diminution in the size of the urinary stream and he had great difficulty in starting it. About a year and half ago pain developed in the right hip, more or less constant, and recently has increased in severity. During the past year he has complained of an increasing weakness.

For about two or three years he has had pain in the right upper quadrant of the abdomen, dull in character, and localized.

Physical Examination.—The patient had a skin cancer of the left ear. Lungs were normal. Heart: The borders were within normal limits, tones clear, regular, no murmurs, excellent quality. Abdomen: The descending sigmoid and colon were readily palpable and there was a moderate swelling in the region of the bladder.

Rectal examination showed good sphincter tone. The prostrate was enlarged one plus, not painful on examination, and its consistency was described as of stony hardness.

Urine: Many pus cells and the cultures showed a group of Gram-negative rods (Eberthella).

Blood: Red cells 5,110,000; white cells, 9,100; hemoglobin, 90 per cent. Blood pressure: systolic, 108; diastolic, 66. Blood chemistry normal.

Roentgen-ray examination revealed multiple irregular areas of increased density in the right upper quadrant between the second and third lumbar vertebræ. A set of intravenous pyelograms showed the presence of a very large hydronephrosis on the right side and in the outlines of the intravenous pyelogram were seen the previously seen stones. Left pyelogram was normal. There was a rather large sella with heavy skull vault and large sinuses. Changes in the pubic bones were compatible with metastases.

Cystoscopic examination revealed a moderate cystitis, mild trabeculation of the bladder and many superficial diverticulæ. There was a large median bar, marked thickening of the interureteric ligament and some shortening of the trigone.

Clinical diagnosis was multiple calculi in the right kidney with a right-sided hydronephrosis, carcinoma of the prostate with bone metastases, chronic cystitis, chronic fibrous myocarditis, generalized arteriosclerosis, epithelioma of the ear.

Because of the severity of the urinary symptoms a transurethral resection was advised, but was refused by the patient.

He was again admitted to the hospital on June 6, 1932. There was marked increase in his urinary symptoms. He had a great deal of pain both during and after urination, a great deal of difficulty in getting the stream started, and he had lost weight.

Rectal examination showed a definite increase in the size of the prostrate, and the consistency was stony hard.

Residual urine, six ounces.

Roentgen-ray examination showed an increase in the metastatic areas in the bones.

On June 14, 1932, a transurethral resection under sacral anesthesia was done. The patient ran a smooth and uneventful convalescence and was discharged from the hospital on June 28, 1932. The pieces of tissue which were removed showed adenocarcinoma of the prostate.

The patient entered the hospital for the third admission on May 14, 1933. He stated that he had complete relief for ten months fol-

lowing the resection. Two months before his present admission the symptoms returned and rapidly became worse. In addition to the urinary symptoms there was great pain in the sacrum and in the upper part of the right leg. Examination at this time showed the persistence of the skin cancer on the left ear, which was still draining. The external genitalia were normal. Rectal examination showed the prostatic bed to be smooth, flat, very hard, and slightly tender. Blood pressure and blood chemistry were normal. Because of great urgency and pain on urination, a second resection was done on May 15, 1933.

Sections removed again showed, as did the previous sections, the presence of adenocarcinoma.

Following the resection the patient had an uneventful convalescence. Twelve days after the operation some shortness of breath and pain in the chest developed. Examination by Dr. Ralph C. Brown showed a small area of bronchial breathing in the right lateral lobe. A diagnosis of pneumonia was made.

The patient died on June 3, 1933. Permission for an autopsy was not granted.

Case 5.—(a) *Papillary Carcinoma of the Bladder;* (b) *Adenocarcinoma of the Prostate;* (c) *Adenocarcinoma of the Colon.*

Dr. J. B. B., aged sixty-nine years, first entered the Presbyterian Hospital, September 17, 1923. Previous history was irrelevant.

Complaints on admission were hematuria and burning on urination. Three months before admission to the hospital the patient noticed gross blood in the urine. He stated the blood was present at the beginning of urination and until the act was completed. He had two attacks of hematuria, the urine being grossly bloody. Burning on urination three weeks before entering the hospital was described as mild and not continuous.

Physical Examination.—The head, neck, heart, and lungs were normal. Liver and spleen were not palpable. Kidneys were palpable; normal in size. External genitalia were normal. Prostate was normal in size and in consistency.

Blood: Red cells, 4,480,000; leukocytes, 10,800; hemoglobin, 80 per cent. Blood pressure, systolic, 138; diastolic, 80. Wassermann findings were negative. Blood chemistry: urea, 48; uric acid, 7.6; creatinine, 1.4; nonprotein nitrogen, 43.

Urine: Albumin and 30 leukocytes per cubic millimeter. Cultures: staphylococcus albus.

Roentgen-ray examination revealed no stone in the urinary tract.

Cystoscopic examination revealed a tumor, the size of a walnut, located behind and above the left ureteral orifice. On the anterior surface of the tumor there was an area of ulceration. There was no evidence of cystitis. Small pieces of tumor were removed with

a cystoscopic rongeur for histologic examination. Pathologic diagnosis: papillary carcinoma.

The patient was advised to have a suprapubic and a wide resection of the tumor.

Operation.—On October 12, 1923, a suprapubic cystostomy was done. Examination of the tumor at the time of operation showed the previously described areas of ulceration and necrosis. Wide resection of the tumor was carried out. The patient had an uneventful convalescence and was discharged on November 4, 1923.

Histologic examination of the pieces of tumor indicated papillary carcinoma.

The patient was asked to report for cystoscopic examination at regular intervals. During a period of eight years, from January 29, 1924, to February 22, 1932, many cystoscopic examinations were made and none showed any sign of tumor.

The patient reëntered the hospital on February 22, 1932, for a check-up. At this time the general physical examination revealed no abnormalities except for an increase in blood pressure, which was 190 over 90.

Rectal examination showed the prostate to be slightly enlarged, very hard in consistency, and the surface decidedly irregular. A diagnosis of carcinoma of the prostate was made.

Cystoscopic examination showed no sign of a tumor in the bladder.

The patient, subsequently, entered the Mayo Clinic in July, 1934, and at this time the diagnosis of carcinoma of the prostate was verified and a transurethral resection performed. The pathologist's examination of the removed tissue revealed adenocarcinoma. A second resection was done in September, 1935. The patient subsequently developed a total obstruction of the bowel, for which Dr. C. W. Mayo performed a resection of the colon. The pathologist's report showed adenocarcinoma, grade 2.

When it became evident to the older clinicians that it was possible for a patient to have two or more independent primary neoplasms, it was imperative, in order to establish this on a rational basis, to set up certain criteria which were to be met and which were to be fulfilled in order to establish the fact that the patient really had two independent primary neoplasms. The first criteria for multiple malignancies were the postulates of Billroth, which were as follows: (1) Each tumor must have an independent histologic appearance; (2) the tumors must arise in different locations; and (3) each tumor must produce its own metastases. To these postulates, Mercanton added a fourth to the effect that, following operative procedure, the patient must remain free of the

disease, thus demonstrating that the growths were independent, since had either one been a metastasis it would be reasonable to assume the presence of other metastases, and the patient would not remain free from evidence of the disease.

Although it would seem that these postulates are somewhat easy of fulfillment, the adverse criticism has been that adherence to them would result in gross error. Nevertheless, they have received so much consideration and discussion recently, possibly due to the interest manifested by both clinicians and pathologists, that the advisability of presenting some of these criticisms is apparent. However, before presenting the various discussions, I should like to call attention to the difficulty in meeting the third postulate. In the first place, the patient may come under observation early in the course of the disease, long before metastases have had time to develop. In the second place, the metastases may be so insignificant that they cannot be demonstrated clinically. If the various cancer campaigns advising the public to seek advice early are to be a benefit or perhaps have already been a benefit, then the patient theoretically should come in before the metastases have developed or before they can be demonstrated. Because these postulates have received a great deal of consideration in recent times it might be well to present briefly some of these opinions.

Seecof criticizes Billroth's postulates as follows:

1. *Difference in histologic appearance.*—(a) The presence merely of different histologic appearance is of little value because of the possible change of type cell in metastases and regional or local recurrences, especially after biopsy or treatment. (b) On the other hand, the absence of different histologic appearances may be of little value on the negative side, because in "system" and "paired organ" instances there may be multiple foci with the same type cell.

2. *Different points of origin.*—(a) That they are found in different locations may be of little value because of possible error in misjudging a metastatic focus in an apparently definite case, especially when the change in type cell is marked. (b) In the absence of different locations a case might well be ruled out were it not for the group of mixed tumors, the so-called sarcocarcinomata, a much disputed group.

3. *Each must produce its own metastases.*—(a) When each primary focus produces its own metastases the case is definitely one of multiple primary neoplasms. To prove that the second apparently primary focus is not a "changed" metastasis from the first may not be possible in a given case by our present methods. (b) Multiple primary malignant tumors may exist without demonstrable metastases.

Warren and Gates observe that adherence to Billroth's third postulate would rule out a very large number of cancers, and as our knowledge of cancer has increased and as our confidence in distinguishing between primary tumor and metastasis has grown, there has been a steady liberalization of these requirements. This, they add, has made for accuracy rather than for inaccuracy, as the former criteria resulted in a falsely low incidence. In their study, Warren and Gates adopted the following stipulations: Each tumor must give a definite picture of malignancy, each must be distinct, and the probability of one being a metastasis must be excluded.

Hurt and Broders, in their study, follow the criteria of Goetze as advocated by Hanlon. These are: (1) The tumors must have the macroscopic and microscopic appearance of the usual tumors of the organs involved; (2) exclusion of the probability of one tumor being a metastasis must be certain; and (3) the diagnosis may be confirmed by the character of the individual metastasis.

In the diagnosis of multiple malignancy the exclusion of the possibility of the second neoplasm being a metastasis may, at times, be one of the most difficult problems.

The group of cases that form the basis of this report are all cases of multiple primary malignant tumors of the genito-urinary system with the exception of Case 4. As a rule, multiple tumors of the genito-urinary tract occur less frequently than multiple tumors in other systems, of which the gastro-intestinal system heads the list. However, in view of the fact that one of the tumors may be located in the urinary system and another in another system as was the case in a patient previously reported in which one tumor was located in the bladder and the other in the male breast, it may be well to bear this possibility in mind. In other words, when patients have a malignant tumor of the urinary tract they may also have another malignant tumor elsewhere; therefore, it

is necessary to discuss in this connection some of the difficulties in the diagnosis of multiple malignancies in other systems besides the urinary tract.

The reports of multiple malignancies in the breasts are open to criticism, the probability of metastasis from the one breast to the other breast being so strong. "That the breast may be the site of independent multiple carcinoma cannot be denied, but proof of true multiplicity is extraordinarily difficult." They feel that most cases where primary gastric and primary ovarian cancers are reported should be discarded "owing to the great ease with which gastric carcinomata metastasize to the ovaries." They discard most reports of multiple ovarian tumors due to difficulty in differentiating between multiple origin and metastasis in such cases. They feel that numerous cases of carcinosarcoma, particularly of the thyroid, are open to suspicion. They omit reports of types of malignancy known to be multiple under ordinary circumstances, such as myeloma and those frequently multicentric in origin as carinoma of the liver.

Warren and Gates are uncertain as to whether certain skin carcinomata, associated with exposure to soot and tar, x-rays, certain of the arsenical dermatoses and xeroderma pigmentosum should be included in what might be termed spontaneous cases of multiple malignancy. They, however, do include a small number of such cases. They feel that multiple carcinomas of the rectum, arising on a basis of polyposis, "are fully as well substantiated as multiple carcinomata of the skin, the independence of which has never been questioned."

In discussing the difficulties encountered in eliminating the possibility of metastasis, Burke stresses that a primary tumor which gives rise to metastases may be so small as to be only located by painstaking microscopic study; yet it gives rise to metastases which are macroscopic. Thus, particularly atypical invasive hyperplasia of the prostatic epithelium may be discovered which has not reached the stage of tumor. He notes that Rich and Moore have called attention to frequency of occult symptomless cancer of this organ.

The problem of eliminating the factor of metastasis is further complicated by the fact that metastases and recurrences may occnr years after the apparent cure of a primary malignancy. Mann re-

ported the following illustrative case: "A woman, in 1904, had a radical operation of the right breast for cancer. She later developed uterine fibromyoma. In 1932 a nodule appeared in the old operative scar, which proved to be scirrhous carcinoma. In 1933 a nodule appeared in the left breast. A radical amputation was done and scirrhous carcinoma was found. There was no involvement of regional nodes." Man thinks it is possible that the nodule found in 1932 may have been a recurrence of the original tumor after a long period of latency (twenty-eight years) and the tumor of the left breast a metastasis. He entertains the idea that this patient possibly furnishes an instance of a "blastomatous diathesis."

Further cases serving to illustrate late appearance of metastases and recurrences are those reported by Holden. Of three patients subjected to radical mastectomy for cancer of the breast, one showed metastases to spine and pelvis ten years later, the second had a recurrence in the skin over the right rectus muscle and pulmonary metastases twelve years later, and the third showed a recurrence fifteen years later. In a fourth case, a carcinoma of the lip was removed, and sixteen years later there appeared a tumor of the posterior mediastinum which proved to be squamous-cell carcinoma, probably a metastasis.

Hurt and Broders, in their discussion of multiple malignancies, stated that few of the reports in the literature include cases in which there were malignant tumors in paired organs or in the same organ because of the difficulty in excluding the possibility that the second lesion was metastatic. They continue:

> "It is known that cysts of the ovary are often bilateral and it is also known that certain types of these cysts often become malignant, so it would seem that in cases of bilateral papillary carcinoma of the ovaries the evidence is in favor of two or more primary growths rather than of metastasis from one ovarian tumor to the other ovary. It is agreed by most authorities that polyps of the intestinal canal are often forerunners of malignant tumors. In cases of multiple polyps in which more than one malignant growth is found, the conclusion would be that two separate malignant growths had developed on two separate polyps. It is hard to conceive of multiple basal cell epitheliomas or widely separated squamous-cell epitheliomas of low grade being produced from a single focus."

Hurt and Broders state that the question concerning simultaneous cancer in both breasts or cancer in one breast subsequent to that in the other is not easily settled. They note that Harrington,

in a series of 3,038 cases of carcinoma of the breast, found twenty in which the condition was bilateral. He considered the growths to have been primary in each breast. In forty-two of the remaining cases, cancer developed in the opposite breast subsequently. In most cases, cancer of the second breast is considered primary by Harrington, except in cases in which the lesion is obviously metastatic.

Kilgore studied 1,100 selected cases of cancer of the breast and found the second breast, in thirty-seven instances, to be the site of cancer either simultaneously or subsequently. In thirteen of these cases, he considered the second lesion to be definitely independent, and after a study of the Census Bureau statistics he concluded that a woman who has had one breast removed for cancer and survives five years after operation is about four times more likely to have cancer in the remaining breast than is the average woman of her age to have cancer of either of her breasts.

Owen calls attention to the occurrence of metastases many years after the apparent cure of the primary growth, but he feels that many of the cases so diagnosed are in reality entirely new and independent malignancies.

Warren and Gates state that their experience leads them to believe that multiple cancers are much more frequently missed than their presence wrongly diagnosed. They add that this is particularly true if resort is not made to microscopic examination of tissues. Moreover, when the second tumor occurs in a case which has been previously cured of carcinoma, it may be missed or the case counted as a single carcinoma unless adequate clinical record is available to the pathologist.

HEREDITY, SEX, AND AGE IN RELATION TO THE OCCURRENCE OF MULTIPLE MALIGNANT TUMORS

Heredity.—Hurt and Broders say that there are many opinions concerning the part that heredity may play in causation of malignant neoplasms in human beings. They note that family histories in most clinical records lack detail and thoroughness and are decidedly inadequate for any statistical data of great value. In their study there was some record of family history in seventy cases. In twenty of these (28.6 per cent) there was a history of malignant tumors in other members of the family. Three patients gave

histories of more than one member of the family with a malignant tumor. In one of their cases, a woman, aged thirty-four, with cancer in one breast, developed cancer in the second breast at the age of thirty-five, and at forty-two developed an abdominal condition necessitating an exploratory laporotomy; at this operation an inoperable malignancy was found in the stomach. This patient's mother and three of her sisters had cancer of the breast.

From the standpoint of heredity, the two cases of multiple primary carcinomas involving the stomach and colon in two brothers reported by Bull (1932) are of great interest. In one case, the occurrence of the two tumors was simultaneous; in the other case, the growth in the colon appeared subsequent to the resection. All four tumors were successfully extirpated.

Sex and Age.—All of the cases reported in this paper occurred in males. The ages were sixty-one, sixty-nine, seventy-nine, eighty-one and eighty-two years. The average age would be seventy-four years.

Hurt and Broders (1933) state that there was nothing of interest in their study as to sex distribution (thirty-two patients male, thirty-nine patients female).

Hanlon (1931) found that the average age of patients with multiple cancers, as reported in the literature, was 58.8 years. In his own series in which autopsies were performed the average age was 62.6 years. Among Owen's cases in which the age was given, the average age was 62.1 years, but Hurt and Broders say he did not take into consideration the age at which the lesions appeared.

In the Hurt and Broders series, the average age at which the lesions appeared was 50.4. They state that difficulty was experienced in some cases in estimating the age at which lesions appeared, and in these cases as a rule the age at the onset of symptoms was taken as the age at which the tumor developed.

Hanlon finds a definite relationship between the occurrence of multiple primary carcinoma and senescence. They occur among persons who are several years older than those who harbor one carcinoma.

In Bugher's study (1934) the incidence of multiple malignancy was 3.6 per cent for males and 1.9 per cent for females, or 3.1 per cent for the entire group of 983 cancer cases at autopsy. In the

series were three cases of triple malignancy (0.45 per cent), all in males.

In forty-six cases of multiple new growths Burke (1936) found thirty-five in males and eleven in females, but qualifies that his entire necropsy series disclosed a two to one predominance of males over females. The age range extended for males from fifty to eighty-four years, with an average of 63.6 years; for females, thirty-eight to seventy years, with an average of 52.9 years. The factor of heredity was positive in fourteen cases (30.4 per cent), negative in twelve cases, and incomplete or unelicited in twenty cases.

Warren and Gates (1932) found that multiple carcinoma occurs at approximately the same age as does single carcinoma. They state that there is no signficant difference in the ages of patients with one, two or more cancers. They are of the opinion that the idea expressed in the literature to the effect that multiple malignancies occur at a more advanced age than do single malignancies is based on inadequate data. In their own series of forty cases of multiple malignancies, representing 3.7 per cent of 1,078 malignant disease autopsies, twenty-five were in females and fifteen were in males. The average age at death was 67.7 years for males, 58.2 years for females, and 61.8 for the entire group. For the patients in their study dying of one cancer, the average age was 59 years for males and 52 years for females, an average of 55.5 years for the whole group.

Of 111 cases of three or more malignancies collected from the literature by Warren and Gates, they found the age and sex stated in eighty-three. Fifty-one of these were males with an average age of 57.9 years and thirty-two were females with an average age of 47.8 years. The authors observe that, in view of the preponderance of cases of carcinoma of the skin in this series and the greater frequency of the lesion in males, it is not surprising that a slight preponderance of males occurs in this series. Unexpected, however, is the age at which these cases were observed. One might well expect such a group to be definitely older than the patients in whom only two tumors were found. Hanlon, on a basis of twenty-four cases of multiple primary carcinoma involving three or more organs, found an average age of 63.6 years. Warren and Gates found the average age of all patients with more than two pri-

mary carcinomas to be 54 years, as contrasted with 55.5 years for all cases of multiple malignancy. They comment that "certainly these cases have not developed their multiplicity of cancers because of a longer time during which additional tumors might make their appearance."

CASES OF MORE THAN TWO MALIGNANCIES IN THE SAME PATIENT

Cases of more than two malignancies in the same individual are exceedingly rare and publications dealing with this subject are few.

Warren and Gates, in 1932, found only three cases of triple or more malignancies in the same individual. In a later report they report a case of a woman, aged fifty-three years, showing the following: Malignant papillary adenocytoma, malignant adenoma of the colon, and metastasizing carcinoid of the ileum. McNamara reported the occurrence of epidermoid carcinoma of the penis, adenocarcinoma of the liver, adenoma of the kidney and basal cell type carcinoma of the skin in a patient who, seven years before, had been operated upon for a rodent ulcer which did not recur. In this connection it might be well to quote the report of Davis, Hanelin, and Mouzakeotis (1936), who reported a case of multiple tumor syndrome including carcinoma of the male breast, pleiomorphic sarcoma of the thigh and neuro-fibromas of the skin in a man, aged fifty-seven years. These authors observe that "as far as they can ascertain there was no relationship between these tumors. Yet the fact that the patient has the ability to form new growths from derivatives of various germ layers gives a new insight into neoplastic tendencies in man. Heretofore, single or multiple growths from the same germ layer have been noted, but the incidence of association of tumors and neoplasms derived from independent embryonal structures has not been extensively dwelt on."

Kulikowska and Hoerner (1934) report a case of carcinoma of the uterus (body), carcinoma of the right ovary, and sarcoma (lymphoblastic) of the left suprarenal gland. The tumors of the uterus and ovary were recognized clinically (at operation); the third malignancy was discovered at postmortem.

Drooker (1937) reviewed the rhinolaryngologic cases of triple cancer in the literature and reported a case of triple primary can-

cer, all of which were within the realm of the rhinolaryngologist He finds that in general triple primary malignancies of miscellaneous organs comprise 2.9 per cent of all cases of multiple malignancies.

Nemours-Auguste, et al, describe a case of three successive primary carcinomas in the same patient. The patient, a man aged sixty-six, was cured of an opithelioma of the nose six years before he came under observation for cancer of the larynx. While under treatment for this condition he suddenly died with hepatic symptoms, proved at autopsy to be due to metastases from an unrecognized cancer of the stomach.

Zylberszac, during an experimental study of the reticulo-endothelial system in mice, found a mouse with an osteosarcoma in a rib and a carcinoma in the kidney. This led him to a search of the literature for the occurrence of carcinoma and sarcoma in the same patient. He found the condition to be extremely rare. He states that multiple growths in general arise in only 1.9 to 3.9 per cent of all patients with malignant disease, and that concomitant carcinoma and sarcoma appear in only 0.84 per cent of these.

Portuondo (1936) reports a case in one patient of hypernephroma of the right kidney with cerebellar metastases, a carcinoma of the pituitary, and an acoustic neurofibroma of the right sixth cranial nerve. The author comments that the hypernephroma and the neurofibroma may have been due to embryonic cell rests.

OBSERVATIONS DEALINGS WITH STASTISTICS ON MULTIPLE MALIGNANCIES

A review of the various statistical studies dealing with the frequency of occurrence of multiple malignancies impresses one with the fact that these studies show a great variation, from 0.3 per cent to 7.8 per cent. Because of these variations and because of the growing interest in this subject, it might be well to mention briefly some of these various figures.

Puhr, in a study of 6,718 necropsies performed over a period of twenty-one years, found an incidence of 0.3 per cent; Murray, in a study of 4,219 cancer cases at Oslo, found 1 per cent, and he concludes that multiplicity of malignant neoplasms is rare. Orr believes that the accurate recording of multiple malignant neoplasms

may decide the disputed question as to whether one malignant neoplasm exercises an inhibitory effect on the development of a second. His figures are too small to settle the issue but tend to show that the incidence of multiple malignant neoplasms is about what would be anticipated if the occurrence were accidental, and Fried believes that the incidence of multiple cancer in a person is merely a matter of chance. Hanlon believes that multiple primary malignant growths are coincidental rather than a response to a definite law of formation of tumors. Mosher believes that a second or even a third primary malignant tumor occurring in one person is simply a coincidence.

Billelo and Montanini found only 0.5 per cent of multiple malignancy.

There seems to be a general feeling that the statistics of the European investigators are too low, since recent publications from this country show a much higher incidence. In regard to the low incidence abroad, Bugher states that it is a well known fact that, since the war, comparatively little microscopic work of a routine nature is performed in European hospitals.

Schreiner and Wehr, at the State Institute for the Study of Malignant Disease, found that primary multiple cancer occurred in 2.7 per cent, and Bugher found an incidence of 3.1 per cent. Burke, in a study of 2,033 autopsies found an incidence of multiplicity of 7.8 per cent, excluding such lesions as lymphosarcoma, leukosarcoma, multiple myelomata.

Warren and Gates, in a study of 1,259 cases of multiple malignancy collected from the literature, to which the add 40, found an incidence of 3.9 per cent. In their own series of 1,078 cancer autopsies the frequency of multiple malignancy was 3.7 per cent. On the basis of all statistics, including the European, the frequency was 1.82 per cent. These authors remark that whether the variation between American and European figures represents more frequent occurrence here, more general study of autopsy tissues here, or some other fact, is difficult to say.

Interesting in this connection is the work of Hurt and Broders, who studied a series of 2,124 patients in whom a diagnosis of malignancy was made by microscopic study. Two years later a review of these patients showed that seventy-one had developed

another primary malignancy. This showed an incidence of 3.4 per cent.

DIAGNOSIS

The vast majority of the recorded cases of multiple malignancies have been diagnosed at autopsy. This fact can be explained in several ways: (1) In many cases the second tumor may be small and, therefore, clinically silent at the time of the death of the patient from the first malignancy, and the condition of multiplicity is only revealed at autopsy or by microscopic examination. (2) When, in the presence of a known malignancy, a second neoplasm is noted it is readily dismissed as an extension, recurrence, or metastasis of the first growth.

White calls attention to the fact that "the infrequency of two simultaneous lesions in an organ has naturally made the search for such a condition, both before and during operation, not a matter of routine, and, as such, cases are usually found by accident rather than by diligent effort."

With the improved facilities for diagnosis and routine employment of modern diagnostic agents, including biopsy examinations, the clinical reports of diagnosis and treatment of multiple malignancies are becoming more frequent.

One might also call attention to the fact that, when a second tumor arises in a patient who already has been cured of one neoplasm, the first and frequently the only diagnosis made is that of metastasis. The suspicion that it may be a new and independent growth is not considered as frequently as it should be at the present time. As our skill in the treatment of malignancies improves, there should be at least theoretically an increasing frequency of this type of patient or case.

SUMMARY

Detailed reports of five cases of multiple primary malignancies have been presented. In three cases the multiple tumors were in the urogenital tract and in one case, one of the tumors was located in the prostate and the other on the ear. The first case was a case of three primary malignant tumors. Studies would seem to indicate that figures regarding the occurrence of these tumors show a greater incidence in the United States than in Europe. These types of cases are probably more common than has been the impression heretofore.

REFERENCES

ABELL, IRWIN: South. Surg., 2:39-46, 1933.
ALCHOWSKY, M. E.: Acta Concrol., 1:563-578, 1935.
BARGEN, J. A., and COFFEY, R. J.: Med. Clin. North Amer., 19:408-410, 1935.
BILELLO, A., and MONTANINI, N.: Tumori, 5:369, 1931.
BILLROTH, C. A. T.: Die Allg. Chir, Path, u. Ther., Berlin, 1863.
BUGHER, J. C.: Am. J. Cancer, 21:809-824, 1934.
BULL, M. P.: Bull. et. Mem. Soc. Nat. d. Chir., 58:1338-1343, 1932.
BURKE, MEAD: Am. J. Cancer, 27:316-325, 1936
CIONI, C., and FUCHS, W.: Riforma Med., 51:512-520, 1935.
COTTINI, G. B.: Dermosifilografo, 9:608-613, 1934.
COUNSELLER, V. S., and BUBSCH, W. C.: Am. J. Obst. and Gynec., 31:628-633, 1936.
DARTIQUES: Bull. et Mem. Soc. de Med. de Paris, 139:84-88, 1935.
DAVIS, G. G., HANELIN, H. A., and MOUZAKEOTIS, T. C.: J.A.M.A., 106:1359-1363, 1936.
DROOKER, J. C.: J.A.M.A., 109:1180-1184, 1937.
EHRLICH, P.: Experimentelle Karzinom—Studienan Mausen, Jena, 1906.
EINAUDI, M.: Cancro., 4:185-188, 1933.
VON FELLENBERG, R.: Helvet. Med. Acta., 2:546-552, 1935.
FISCHER-WASELS, B.: Deutsche Med. Wchnschr., 59:1489-1494, 1933.
FRANCOIS-DAINVILLE, E.: Ann. d'Anat. path., 14:255-258, 1937.
FRIED, D. M.: Arch. Path., 5:565-578, 1928.
FRIEDMAN, A. B., and GOLDEN, M. G.: Radiology, 27:497-498, 1936.
GARDNER, W. V., STRONG, L. C., and SMITH, G. M.: Am. J. Cancer, 26:541-546, 1936.
GIANNINI, D.: Ann. di Ottal. e clin. ocul., 62:852-868, 1934.
GOLDSTINE, M. T.: Am. J. Obst. and Gynec., 30:143-144, 1935.
GORIAINOWA, R. W., and SCHABAD, L. M.: Ztschr. f. Krebsforsch, 33:594, 1931.
GREENWOOD, E. J.: Brit. M. J., 2:538-539, 1936.
GREENE, H. J.: Am. J. Obst. and Gynec., 31:660-663, 1936.
HANLON, F. R.: Am. J. Cancer, 15: (Supp.) 2001-2012, 1931.
HARTMANN, H.: Bull. Acad. de. Med., Paris, 114:480-487, 1935.
HOLDEN, W. B.: Surg. Clinics North America, 13:1393-1394, 1933.
HUGUENIN, R., BRIAN-GARDIELD, P., and BOUCABEILLE, O.: Bull. Assoc. franc. p. l'etude du cancer, 25:621-628, 1936.
HUNT, V. C., and BUDD, J. W.: Surg. Clinics North Amer., 13:1399-1461, 1933.
HURT, H. H., and BRODERS, A. C.: J. Lab. and Clin. Med., 18:765-777, 1933.
JACOB, M.: Ann. d'otolaryng. pp. 320-324, March 1936.
JENSEN, C. O.: Centralbl. f. Bakteriol., 34:28, 1903.
JOLL, CECIL: Transactions M. Soc. London, 55:45-47, 1932.
JUNGHANNS, H.: Ztschr. f. Krebsforsch, 29:623, 1929.
JUDD, E. S., and PHILLIPS, J. S.: S. Clin. North America, 14:525-528, 1934.
KILGORE, A. R.: J.A.M.A., 77:454, 1921.
KRETSCHMER, H. L., and HECKEL, N. J.: Am. J. Surg., 26:387-390, 1934.
KULIKOWSKA AND HOERNER: Bull. Soc. d'obst. et de gynec., 23:662-665, 1934.
KORBLER, J.: Arch. f. klin. Chir., 170:505-507, 1932.
KURU, M.: Arch. f. klin. Chir., 187:79-86, 1936.
LO VULLO, B.: Quaderni radiol., 6:354, 1935.
MAJOR, R. H.: Bull. Johns Hopkins Hosp., 29:223, 1918.
MANN, G.: Polyclinics, 40:1013-1014, 1933.
MASSON, J. C.: Proceedings Staff Meetings Mayo Clinic, 11:395-396, June 17, 1936.
MAYO, C. W.: Proceedings Staff Meetings Mayo Clinic, 11:165-166, March 11, 1936.
MAYO, C. W., and ZELLHOEFER, H. W. K.: Proceedings Staff Meetings Mayo Clinic, 11:525-527, Aug. 12, 1936.

MAYO, C. W., and ZELLHOEFER, H. W. K.: Proceedings Staff Meetings Mayo Clinic, 11:622-624, Sept. 23, 1936.
McGIBBON, J. E. G.: Lancet, 2:806-807, 1933.
McNAMARA, W. L.: J. Lab. and Clin. Med., 29:269-274, 1933.
MOSHER, H. P.: Discussion of paper by Drooker, J. C.
MURRAY, J. A.: Lancet, 2:800-804, 1927.
NEMOURS-AUGUSTE, D., and BONHOMME, D.: Bull. Assoc. franc. p. l'etude du cancer, 25:629-631, 1936.
ORR, J. W.: J. Path. and Bacteriol., 33:283-290, 1930.
OWEN, J. L.: J.A.M.A., 76:1329-1333, 1921.
PEMBERTON, J. DE J., and WAUGH, J. M.: Surgery, 2:211-214, 1937.
PORTUONDO, B. C.: Am. J. Cancer, 28:752-759, 1936.
PUHR, L.: Ztschr. f. Krebsforschr., 24:38, 1926.
RICHE, V., MOURGUE-MOLINES, E., and GUIBERT, H. L.: Bull. Assoc. franc. p. l'etude du cancer, 24:280-310, 1935.
SASAKI, H.: Gann., 30:344-345, 1936.
SEECOF, D. P.: J. Cancer Research, 8:213, 1924.
SCHREINER, B. F., and WEHR, W. H.: Am. J. Cancer, 20:418, 1934.
SUGIURA, R., and BENEDICT, S. R.: J. Cancer Research, 10:194, 1926.

ENDOTHELIOMA OF THE CORPORA CAVERNOSA

GORDON S. FOULDS, M.D., F.R.C.S.(C)

Toronto, Ontario, Canada

The corpora cavernosa are not commonly the site of malignant disease. They may be secondarily invaded in epithelioma of the penis or urethra as was recently reported by Stevens and the author, and the deposit of metastatic growth in the corpora has been noted by Frontz, Begg, Garofola and others, but the development of a primary malignant endothelioma is very rare. Only six such cases appear in the literature. I shall review each of these six cases very briefly and report in greater detail a seventh case seen at St. Michael's Hospital.

Maurer used as the subject for his dissertation at the University of Halle in 1883, the case of a man, fifty years old, suffering from an infiltrating tumor of the penis with metastases to both inguinal regions. The patient had noted the swellings in the groins for three months and these tumors had been incised some time before. He was not conscious of any diseased condition of the penis but examination showed that it was swollen, in a state of semi-erection and extremely rigid as though made of wood, but no changes in form were noted.

Autopsy revealed no changes worthy of note in the internal organs, aside from an abscess in the right iliac fossa, which developed following an incision into the inguinal tumors and extended downward as far as the neck of the femur. There were numerous hard nodules the size of pin-heads in the skin and just-under it. The corpora cavernosa of the penis and the urethra were thickened and of practically uniform hardness.

Alexander and Dunham, in 1897, reported the case of a man, aged fifty, who, for six months, had noted a painless lump in the dorsum of the penis. This caused upward curvature of the organ during erection which made intercourse impossible. At operation on June 6, 1894, the tumor, which was not encapsulated, was dissected out. The patient had no recurrence when examined twenty-eight months later. He died about three years after the operation, cause unknown.

Hildebrand was consulted in 1898 by a man, sixty-eight years

old, regarding a tumor which he had discovered one year previously in the free portion of his penis. The only symptom was a troublesome dribbling after micturition. In the pendulous portion of the quite long penis, on the under side, somewhat toward the left and approximately midway between the corona and the scrotal attachment there was a tumor the size of a pigeon's egg. By palpation it was as hard as cartilage and had no connection with the skin, so that the latter was freely movable. The surface of the tumor was smooth. Patient desired removal of the tumor but not amputation of the penis. Hildebrand therefore decided upon extirpation of the tumor and thought the chances of success were fairly good because of the hardness of the tumor. The penis was drawn forward tensely and the blood supply cut off with a rubber tube. On the lower side the author made a longitudinal incision extending from the corona glandis to the scrotal attachment. After pushing the skin aside he came upon the tumor, which seemed to be located within the corpora cavernosa. It was found, however, that the tumor lay so close to the urethra that a segment of the latter would have to be excised along with the tumor. The two corpora cavernosa of the penis and the urethra were severed transversely above and below the tumor and extirpated, so that only small rests remained. The length of the segments of corpora cavernosa was 4 to 4.5 cm., while the excised segment of urethra measured 3.5 cm. The urethra was not involved by the tumor. A satisfactory result was recorded with no recurrence six months later.

Colmers, in 1903, described an endothelioma of the corpus cavernosum occurring in a miner, fifty-six years old. Two months before examination the patient had noted that erection was painful, and during this period there had been constant pain, more severe at night. On the dorsum of the enlarged and rather rigid penis there were several hard subdermal nodules, the size of peas, as well as firm linear thickenings. The swelling extended to the perineal region, which was hard with infiltration. The inguinal lymph glands showed no marked enlargement and there was no particular sensitivity to pressure. Micturition was undisturbed. The urine was clear and free from blood, pus, albumin, and sugar. Amputation failed to relieve the pain and death followed in a week after operation.

Balog and Cerqua report the case of a man, forty years old, who, for two years, had suffered from pain at the root of the penis and during this time had been aware of a small tumor in that region. The pain increased and was especially unbearable in connection with erection, so that finally he was no longer able to practice coitus. The tumor noticeably increased in size.

The penis was medium-sized and showed no particular visible change. Palpation revealed a smooth, roundish tumor, the size of a pea, at the root of the penis, near the anterior surface, somewhat toward the left. The skin was firmly adherent to the underlying tissue. From the urethra no secretion could be expressed. The inguinal glands were not enlarged. Endoscopic examination revealed that the urethral mucosa was normal and had no connection with the tumor. In the urine there were traces of albumin. Wassermann and Sgambati reactions were negative.

At operation it was found that the skin and the fascia of the penis were completely uninvolved. The tumor lay in the corpus cavernosum. The tunica albuginea of the latter was split and since the tumor could not be enucleated by blunt procedure it was removed with shears. In spite of attachments on all sides its fibrous capsule remained uninjured. The wound in the corpus cavernosum was sutured and the patient left the hospital with the wound healed by primary intention ten days after operation.

Yamamoto, in 1930, reported the case of a fifty-eight-year-old farmer who reported that during the early part of December, 1928, he suffered minor injury to the external genitals and the perineum. About two weeks later he noticed a slightly painful nodule, about the size of the tip of the forefinger, at the root of the penis; this nodule gradually spread in a distal direction, so that the organ finally was transformed into a hard rod. The patient was always conscious of slight dull pains in the penis and upon palpation these pains became more distinct. In May, 1929, he developed symptoms of stenosis in the urethra.

On examination, the organ was very stiff, showed livid discoloration, and was curved upward so extensively that it almost touched the abdomen. The skin of the penis showed marked edematous swelling and a number of stricture rings. The consistency of the corpus cavernosum was as hard as a board throughout and when it was touched the patient always complained of

severe pain. The urethral orifice and the anterior urethra were very narrow, so that only the very finest sound could be passed into the bladder. The urine was very cloudy and contained many pus cells. The prostate was of normal size and consistency, with smooth surface and no sensitivity to pressure. The Wassermann reaction was negative and there was slight leukocytosis.

Total amputation of the penis according to the Thiersch-Gould method was done. The total weight of the extirpated shaft of the penis was 130 grams. Strange to say, hemorrhage was very slight from the corpora cavernosa of the penis during the operation. The surface of the cut shaft of the penis had a medullary appearance and was not at all rich in blood. The corpora cavernosa seemed, by macroscopic examination, to have been transformed into a solid mass.

C. W., a groom, forty-five years of age, was admitted to St. Michael's Hospital on June 21, 1922. He had been in excellent health, and had suffered from no illness except scarlet fever, until February, 1922, when he developed influenza. Since then he had suffered from cough, night sweats, and pain in the right side of his chest, and had been a semi-invalid. A short time before admission he had taken some patent "nerve medicine" and fifteen minutes later had a severe convulsion. When admitted, he was still unconscious and clonic convulsions were occurring over the whole of the body about once every minute. After half an hour the convulsions became limited to the left side and shortly ceased, the patient remaining in a comatose state.

On examination, there was a slight flaccidity of the left arm and leg and a slight paresis of the left side of the face. Resonance was reduced over the lower part of the right chest and râles were heard on both sides. The external urethral orifice was small. The temperature was 100, the pulse rate 88. No other abnormalities were detected. The urine was normal. The following day he was conscious but drowsy. He was discharged on his own request on the fifth day.

On July 21, 1922, the patient was admitted to the Toronto General Hospital complaining of pain in the right chest. The area over the lower lobe of the right lung was dull to percussion and a small quantity of fluid was withdrawn from the right pleural cavity. Examination of this fluid and of the sputum was negative for tubercle bacilli. Slight convulsive seizures occurred on August 8, and on September 28 the cerebrospinal fluid contained eight cells per cubic millimeter and the globulin reaction was negative. There were no symptoms referable to the genito-urinary system and on ordinary physical examination no abnormalities were detected in it. The patient was discharged October 21.

On June 27, 1923, he was readmitted to the Toronto General

Hospital complaining of weakness, cough and constant pain in the lumbar region. This pain was aggravated by movement and sometimes radiated down the left leg. He was not able to sit up in bed. On examination, râles were present and decreased resonance was elicited over the lower right chest. There was marked limitation of movement in the lumbar spine and tenderness was complained of on pressure over the lumbar vertebræ.

Around the border of the glans penis an indurated, reddish-tender area was noted. The induration extended back along the whole length of the corpus cavernosum urethræ as a hard nodular cord. There was no apparent involvement of the corpora cavernosa penis, nor of the inguinal lymph glands.

Examination of the sputum and of fluid removed from the right pleural cavity did not reveal the presence of tubercle bacilli. The Wassermann reaction was negative on each of three examinations. Roentgenograms of the chest showed parenchymatous changes in both upper lobes of the lungs. The right lower lobe was so densely clouded that detail was obliterated. Roentgenograms of the spine showed localized rarefaction in the body of the third lumbar vertebra. A diagnosis was made of carcinoma of the urethra with secondary involvement of the third lumbar vertebra.

On November 2, 1923, he was readmitted to St. Michael's Hospital in a serious condition due to pain, weakness, sleeplessness, cough and shortness of breath. Shortly after admission he had a convulsive seizure which lasted twelve minutes. He had voluntary movements in both legs, but pain in the back was too severe to permit the weight of the body to be borne. There was a kyphosis of the lumbar vertebræ. The knee jerks were exaggerated, and there was a Babinski's sign on the left side. The chest showed reduced resonance, bronchial breathing and râles over the right side. There was a slight elevation of the temperature and the pulse rate with cyanosis and dyspnea.

The glans penis was hard; two large deposits were present in the corpora cavernosa penis and the corpus cavernosum urethræ was a mass of firm, irregular nodules which extended back to the prostate and were particularly marked in the perineum. The prostate was small and the left seminal vesicle firm and palpable. Roentgenograms of the spine, at this time, showed collapse of the body of the third lumbar vertebra. The other vertebræ showed no definite evidence of a destructive process.

On November 18, marked dyspnea developed suddenly. A spontaneous pneumothorax occurred on the right side with complete collapse of the upper lobe. Three days later there was a severe epileptiform seizure and the following day the patient died.

At autopsy the penis was semi-erect, its glans was pale in color, very firm but of normal outline. The external urethral meatus was abnormally small. The corpus cavernosum urethræ was woody in consistency, with a series of nodular masses about 5 mm. in diameter

along its length. The corpora cavernosa penis were firm and indurated and contained several nodular masses.

The mucous membrane of the urethra was intact throughout and cross section of the penis showed an unaltered anatomic arrangement. Throughout the corpora cavernosa penis and infiltrating the corpus cavernosum urethræ were masses of firm, greyish tissue containing multiple minute hemorrhagic areas. A large, firm nodule was situated anterior to the prostate and surrounded the urethra in its bulbous portion. The prostate and bladder were normal. There was no change in the inguinal, sacral, lumbar and other lymph glands.

Throughout the left pleural cavity were fibrinous adhesions, and surrounding the apex of the lung, firm, fibrous bands. The lung showed apical scarring, was intensely edematous and contained very numerous patches of bronchopneumonia. Scattered throughout the lung tissues were numerous firm, white or greyish, distinctly circumscribed deposits, varying in diameter from a few millimeters to a centimeter.

The right pleural cavity was almost completely obliterated by firm fibrous adhesions; the pleura was greatly thickened and the lung appeared almost completely airless. Throughout the collapsed lung tissue were numerous firm, greyish deposits similar to those present in the left lung.

The liver showed a diffuse yellow mottling, and scattered throughout the organ were many firm, white or greyish circumscribed deposits, varying in diameter from a few millimeters to two centimeters. The larger deposits showed umbilication. The spleen was normal in size and appearance but for the presence, in the lower pole, of a firm, circumscribed deposit two centimeters in diameter. The kidneys were normal in size and appearance but contained a few small nodules scattered throughout the cortex of each organ.

In the brain there was a single firm, greyish tumor mass, two and a half centimeters in diameter, in the left cerebrum, close to the occipital pole. Throughout this tumor mass were numerous, very small, hemorrhagic areas.

Microscopic examination of the tissue of the penis showed the arrangement of the tunica albuginea, urethral mucosa and glands of Littre to be normal. The outstanding feature of the tissue was the presence of masses of cells, filling or partially filling the cavernous spaces and also present within the blood vessels of the fibrous trabeculæ, of the tunica and of the subcutaneous areolar tissues. There was some variation in the cells as to size, shape and staining properties. The majority were polyhedral or oval, but a few appeared flattened or cylindrical; their cytoplasm was clear, slightly granular with a large round or oval centrally-placed nucleolus.

In the center of many of the larger masses the tumor cells had undergone degeneration leading to loss of cell outline and breaking up of the nuclear chromatin. Sections stained with Scarlach red

showed abundant fatty droplets throughout the degenerated areas. Areas of hyaline transformation were also to be seen within the cell masses, in the fibrous tissue between the cavernous spaces, and also in the walls of certain of the arteries. In places the cell masses plugging the blood channels or arteries appeared to have become canalized, so that their central portions were occupied by intact, and presumably circulating, red blood cells. Where the tumor cells had lain in contact with the intima of the arteries the endothelial lining had

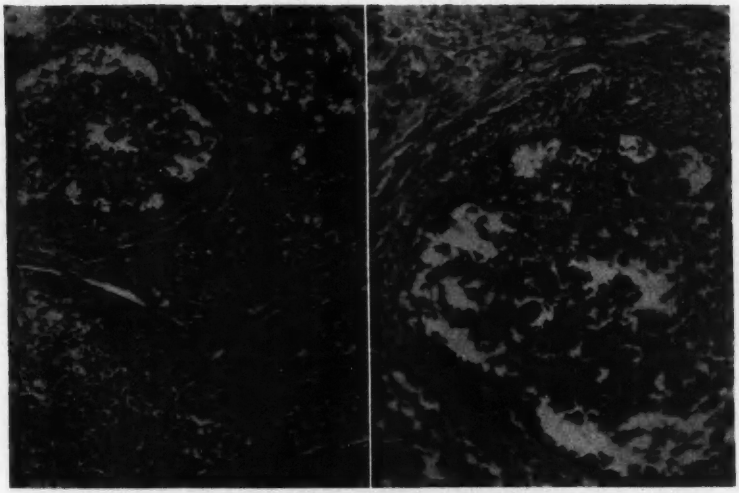


Fig. 1 *(left)*. Cross section through the penis. The blood spaces of the corpus penis are seen to be occupied by masses of tumor cells traversed by channels containing red blood cells.

Fig. 2 *(right)*. High power of portion of tissue shown in Figure 1. The tumor cells appear to spring from the lining cells of the blood spaces.

disappeared, but nowhere was there any indication of infiltration of the media (Figs. 1 and 2).

A striking appearance, which would appear to support the view that the tumor cells were endothelial in origin, was to be seen in many of the undegenerated cell masses. Through these ran circular or irregular-shaped capillary-like channels which appeared to possess a definite lining of tumor cells which sent out twig-like processes to unite with similar processes from neighboring cells, the spaces thus formed having been occupied by intact red corpuscles.

Nowhere in these sections was there any infiltration by the tumor cells through the vessel walls. There was a complete absence of fibrous overgrowth, and evidence of inflammatory reaction was con-

fined to a few small areas in the areolar tissue in which there was a scanty lymphocytic infiltration around the smaller arteries.

In the lung tissue the secondary deposits were seen to be composed of cells identical with those of the primary growth. Here, again, one noted the absence of any fibrous overgrowth and leukocytic infiltration. On the edges of the tumor mass the pulmonary alveoli could be seen with their walls apparently wholly intact, although many of them were filled with tumor cells which appeared to be

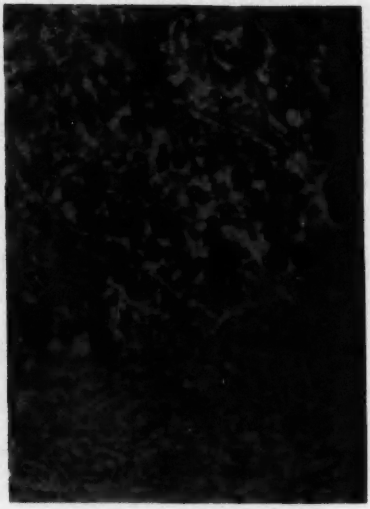


Fig. 3. Section through a metastasis in the brain, showing infiltration of brain tissue.

gradually extending into other alveoli of the same air sac. A common appearance was that of a blood vessel completely filled with tumor cells and surrounded by normal lung. In one of the larger vessels the tumor cells were adherent to the wall and extended into the lumen of the vessel like a trestle work, the interstices of which were occupied by red blood corpuscles. In one section a bronchus was to be seen with a wall which was intact except that the normal cuboidal epithelium was missing from about one-sixth of the circumference, and to this area was attached a compact mass of tumor cells which almost completely filled the lumen. In addition to these tumor deposits there were many areas which showed a typical acute bronchopneumonia process.

Sections through the tumor mass in the brain showed it to be com-

posed of cells also identical with those of the primary growth. Here there was a vague suggestion of an alveolar arrangement, fine trabeculæ dividing small groups of cells into more or less circular and longitudinal masses. The apparent mode of extension of the growth was clearly indicated where, just beyond the margin of the main tumor mass, small, apparently capillary channels were to be seen containing from one or two up to ten tumor cells within their lumen. Canalization of the cell masses and areas of hyaline degeneration were also to be seen in these sections (Fig. 3).

Sections of the tumor nodule in the spleen also showed canalization of the tumor mass by circulating blood. Large areas of hyaline degeneration of the tumor cells were to be seen in this situation.

The tumor growth in the liver possessed the same general characters as already described in the primary growth and in the other secondary deposits. A study of the margin of the tumor showed the cells spreading along the blood sinuses between columns of liver cells. In this situation there was some difficulty in distinguishing with certainty between the tumor cells and the liver cells, as in places the latter had undergone a peculiar, presumably pressure change, associated with the disappearance of the normal, strongly acidophile cytoplasm and its replacement by a clear or slightly granular cell body.

The nodules in the kidneys presented an appearance which differed somewhat from that of the deposits in the other organs. The picture here was that of large areas of degenerated tissue traversed by blood vessels filled with tumor cells; many of the latter showed polymorphous nuclei often pyknotic, and varying greatly in size. Here and there giant cells with multiple nuclei were to be seen. The line of demarcation between the normal kidney tissue and the invading cell mass was very indefinite; there was no round-celled infiltration or fibrous tissue proliferation at the periphery of the growth.

The glands of the prostate were, for the most part, dilated, and in places showed considerable proliferation and desquamation of the lining cells. In certain sections large venous channels at the periphery of the gland were seen to be occupied by tumor cells identical with those of the primary growth. Nowhere was there any invasion of the prostatic tissue proper by these tumor cells.

It is impossible to draw any general conclusion from so few cases. In three of seven cases of endothelioma the tumors were slow-growing with no evidence of metastases. They were resected and the patients recovered from the operations, one living nearly three years and one well five months after the resection. No postoperative observation was recorded in the third. The remaining four patients suffered from more rapidly growing extensive growths

and though one was successfully operated upon, no follow-up was reported.

In the six cases previously reported the microscopic findings were essentially the same as those noted in the case now reported. The classification of this growth as a malignant endothelioma of the corpus cavernosum is based upon the general characters and mode of tension rather than upon the appearance of the individual cells. The urethra was not involved, therefore primary tumors of the urethra can be excluded. The following outstanding characteristics are of importance in support of the diagnosis of endothelioma.

1. The apparent origin of the tumor from cells lining the blood spaces of the corpus spongiosum.

2. The slight invasive powers of the tumor cells which showed a marked tendency to respect the boundaries of the blood vessels in which they lay; infiltration through the vessel walls with fibrous tissue overgrowth and reactive inflammation in the perivascular tissues were almost completely absent.

3. The tendency to canalization of the plugged vessels associated with the formation of capillary-like channels through the mass.

BIBLIOGRAPHY

1. Alexander, S., and Dunham, E. K.: Endothelioma of the corpora cavernosa, Jour. Cut. and G.-U. Dis., 15:247-251, 1897.
2. Begg, R. C.: Persistent priapism due to secondary carcinoma in the corpora cavernosa. British Med. Jour., 2:10, 1928.
3. Colmers, Franz: Ueber, Sarkom und Endotheliome des Penis. Ziegler's Beitr. z. Path. Anat., Jena, 24:295-330, 1903.
4. Balog, Paul, and Cerqua, Saverio: Endotheliom de Corpus Cavernosum Penis. Arch. f. Dermat. u. Syphil., Berl., 161:86-91, 1930.
5. Foulds, G. S., and Stevens, B. W.: Carcinoma of the penis. Brit. Jour. Urol., 9:368-371, 1937.
6. Frontz, W. A., and Alyea, E. P.: Priapism of unusual etiology. Jour. Urol., 20:135-141, 1928.
7. Garofola, F.: Priapism du Tumore Metastatico dei Corpi Cavernosi del Pene. Arch. Ital. di Dermatol., 4:20-32, 1931.
8. Hildebrand: Ueber Resection des Penis Wegen Eines Endothelioma Intravasculare. Deut. Ztschr. f. Chir., Leips., 48:209-222, 1898.
9. Maurer, M.: Uber einem Eigenthuemlichen Fall von Angiosarkom (Endothelioma Intravascular). 1883. (Quoted by Colmers.)
10. Yamamoto, Kinzaburo: A rare case of priapism induced by intravascular endothelioma of the corpora cavernosa of the penis. Jap. Jour. Dermat. and Urol., Tokyo, 30:50-57, 1930.

DISCUSSION

DR. ARCHIE L. DEAN (New York, N. Y.): I can't agree that the experience at Memorial Hospital with multiple tumors has been as high in frequency as the 7 per cent which has been found elsewhere in this country. We have a book in which is recorded the multiple tumors after they have been proved histologically. At present there are between 500 and 600. The most common multiple occurrence that we have seen in the department of urology has been the combination of carcinoma of the lip and carcinoma of the penis. There have been six such cases.

It is interesting, in regard to diseases of the penis, that some of the rarest types of tumor affect this organ. Dr. Foulds reports the fifth endothelioma of the corpus cavernosum. I have treated one similar patient within the last year. There have been five cases of melanoma of the penis reported, the fifth reported last year by Dr. McKenna. We have seen two of those.

Another cancer of the penis which has not been reported as yet is Kaposi's angiosarcoma. Strangely enough, we saw two patients with this disease within six weeks.

DR. WILLIAM F. BRAASCH (Rochester, Minn.): I merely wish to call attention to an observation made by Dr. Broders regarding the fact that after a removal of a tumor an apparent change in grade of malignancy is occasionally noted with recurrence. For instance, a tumor of the bladder with a grade 1 or 2 may be reported, and a subsequent recurrence will frequently be reported as grade 3 and 4. Dr. Broders believes that, instead of a change in degree of malignancy of the tumor, these recurrences are independent tumors. If that is true, the incidence of multiple coincident tumors should be greater than that which Dr. Foulds reported.

DR. BENJAMIN S. BARRINGER (New York, N. Y.): Dr. Foulds' case report is very interesting. I have never seen a primary endothelioma of the corpus cavernosum, but I have seen and was very badly fooled with a metastatic growth of the corpus cavernosum. About two years ago a patient came in with a history of carcinoma of the antrum which was well under control. He had

a growth of about two or three centimeters, connected with the corpus cavernosum. I didn't think of it as metastatic. I cut down and removed a tumor mass attached to the corpus cavernosum. It proved to be the same type as the antrum growth. It was subsequently treated by x-ray. About six months later, the carcinoma of the antrum became active and the patient died within a year. The corpus cavernosum remained apparently normal.

I think that Dr. Kretschmer has called our attention to a very interesting fact in these multiple growths. I remember one of the most amusing instances I have had—a little tragic. The patient had an infiltrating carcinoma of the bladder, which was treated with radium and which was controlled for five years. At the end of perhaps four and a half years jaw carcinoma developed. That was treated and controlled. At the end of about five and a half years after I originally saw him, the patient died of chronic renal disease. Both tumors were under control. The patient died of something else!

PATHOLOGIC ASPECTS OF EXPERIMENTAL ANILINE TUMORS IN THE BLADDER OF FEMALE DOGS

W. C. HUEPER, M.D.

Scarsdale, New York

The complete and definite proof for the existence of an industrial cancer rests upon two types of evidence. The first kind is of medical-statistical nature, being based upon the excessive incidence of a particular type of malignant tumor among a certain group of workers. The value of such data is that of circumstantial evidence. The experimental reproduction of the suspected occupational neoplasm in animals, under conditions resembling those to which the affected workers are exposed, furnishes the direct and conclusive evidence.

There exists satisfactory and sufficient evidence of clinical character for the occupational etiology of the so-called "aniline tumors" of the urinary bladder, occurring mainly in dye-workers, dye-grinders, dyers, chemists and others coming in contact with certain aromatic amines (aniline, benzidine, beta-naphthylamine and their homologues and derivatives). Since 1895, the year of their discovery by Rehn, approximately 550 cases of this industrial neoplasm have been placed on record in the different countries (Germany, Switzerland, Austria, Russia, England, United States and Italy). One American chemical concern alone has contributed to this number, during the last five or six years, approximately one hundred cases. The disease has spread during the last two decades from Germany and Switzerland, to which it was primarily confined, to England, Austria, Russia, United States and Italy, following the development of large chemical industries in these countries after the World War.

The incidence of these tumors among the dye workers employed was estimated by Rehn to vary between 0.2 and 0.4 per cent. According to Gehrmann it is 4.1 per cent and according to recent figures of di Maio more than 20 per cent. The actual frequency, however, is much higher, if these statistical data are properly corrected as to workers appreciably exposed in regard to intensity and duration, and in operations where massive contact

takes place and little precautionary measures are taken, may reach as high as 80 to 90 per cent of the workers employed in the hazardous work for periods exceeding more than twelve years.

The experimental evidence so far available, until recently, was not quite convincing. There were the experiments of Schaer and those of Perlmann and Staehler, who claimed to have produced bladder tumors in rabbits by prolonged exposure to certain aromatic amines. But in both instances doubts were voiced as to the reliability of their interpretations of the observations made. The experimental results reported by Perlmann and Staehler, moreover, could not be confirmed by Berenblum and Bonser and Hueper, Briggs and Wolfe. It was therefore pertinent to develop a method of production by which experimental aniline tumors of the bladder could be readily obtained in the majority of animals used. I believe that this has been accomplished by the investigations to be reported.

REPORT OF EXPERIMENTS

Sixteen mongrel female dogs were used in the experiment. They received during the first twelve months of the experimental period daily subcutaneous injections of up to 15 mgm. of commercial beta-naphthylamine hydrochloride. As periodically performed cystoscopic examinations did not show at the end of this first year any signs of pathologic lesions in the bladder, the dogs were placed on an additional oral medication of from 100 to 450 mgm. of beta-naphthylamine daily. The first evidence of a neoplastic response to the treatment given was discovered at a cystoscopic examination performed twenty months after the start of the experiment. Two dogs showed, at that time, numerous proliferative lesions of preneoplastic and neoplastic nature. During the succeeding twelve months (ending January, 1938) similar mucosal newgrowths appeared in twelve additional dogs, while two dogs remained essentially normal up to that time.

Gross Pathology.—There were, in the beginning, usually only one or two pathologic lesions present in the bladder of the individual animals, but their number as well as size increased with the duration of exposure. At the same time definitely neoplastic manifestations became more frequent. Multiplicity of lesions was therefore a striking characteristic in the majority of cases, attaining, in several instances, a condition of generalized papillomatosis, which, during more advanced stages, greatly narrowed the lumen of the bladder of several dogs (Fig. 1).

The greater number of the pretumorous and tumorous formations were located in the dependent parts of the bladder, where also the largest tumors were found, *i.e.*, at the dome and distal anterior wall.

Tumors located on the proximal portion of the posterior wall and on the base were rare and occurred usually only in a viscus with more or less generalized papillomatosis. The vesical mucosa intervening between the pathologic lesions was, in the less advanced cases, generally smooth and white, but showed in cases of more diffuse involvement a congested and edematous appearance and hemorrhagic areas, intermingled with pin-head sized, whitish thickenings.

Fig. 1. Bladder with numerous benign and malignant papillomatous tumors. The lumen of the bladder had been reduced to a narrow canal.

The pathologic lesions observed may be divided according to their character and appearance into three groups:

1. *Transient inflammatory and vascular reactions.*—The most frequent and earliest pathologic manifestations were represented by well defined "hemorrhagic spots." These consisted, as a rule, of localized convolutions of engorged capillaries, to which occasionally highly hyperemic and tortuous larger vessels extended in radiating formation. In other instances the red stipplings were definitely hemorrhagic extravasations. Multiplicity and group formation were striking characteristics of these lesions. Areas of bullous edema were rarely seen. In a few instances there were also small sloughing ulcers. The mucosal hemorrhagic spots were frequently of highly transient nature and disappeared without leaving a trace, so that it appears improbable that these vascular manifestations represent precancerous lesions. They are most likely acute vascular reactions of chemotoxic origin.

2. *Localized mucosal thickenings.*—These were well circumscribed orange to brown-red or blanched areas, with or without elevation, showing, occasionally, tiny raised points, which, on subsequent examinations, often definitely had the appearance of early papillomas. The

surfaces of these foci were sometimes rough and bled easily. Spontaneous regression of this type of lesion was observed repeatedly, but more often there occurred progressive development into a tissue response that was definitely neoplastic. In contradistinction to this, tumors also appeared in areas which had not shown evidence of preceding mucosal abnormalities.

3. *Tumors.*—The neoplastic proliferations were usually of a papillomatous type. Many were pedunculated; others were sessile and of broad base. Many of the early lesions had the appearance of small edematous mucosal polyps. The well developed papillomatous growths were, in general, composed of rather plump villi, sometimes showing dark red hemorrhagic tips or sloughing lesions. Delicate, feathery papillomas were uncommon. Infiltrative nodular tumors were observed in several instances. The tumors were soft in consistency and very friable. Larger tumors presented cauliflower-like masses measuring up to 3 cm. in diameter and 1 cm. in height.

Microscopic Pathology.—The microscopic examinations of the biopsies and bladder sections revealed the presence of a great variety of epithelial, fibro-epithelial and vasculo-connective tissue changes, many of which having resulted in the grossly manifest lesions described, others being of purely microscopic nature.

The non-neoplastic lesions observed in the bladders of the dogs may be divided into the following types:

1. Inflammatory reactions (simple, ulcerative or polypous).
2. Intra-epithelial abnormalities.
3. Leukoplakia (simple, papillary and infiltrative).
4. Mucous polyps (simple, papillary and infiltrative).

1. *The chronic inflammatory reactions* occasionally observed and cystoscopically characterized by the presence of small, reddish edematous elevations, sometimes surrounding a small mucosal defect or assuming the shape of a short polypous or warty protrusion, were often lined by an atrophic, pyknotic and vesicular epithelium. This showed not infrequently smaller or larger defects filled in by a chronic granulation tissue or leaving a bare fibrous tissue. The loose subepithelial connective tissue contained usually a mild to moderate infiltration of lymphoid and not infrequently also of eosinophilic cells. Loose eosinophilic accumulations occasionally filled the subepithelial capillaries which penetrated through a highly edematous subepithelial zone into an indistinctly demarcated epithelial lining. The submucosal vascular network was often dilated and denser than normal, while varicose and ectatic capillaries were commonly found in the polypous protrusions, and were often the site of smaller or larger intracapillary or vascular endothelial granulomas and obliterations.

These inflammatory reactions did not seem to play any essential or important part as precursors of the development of neoplastic conditions. Their occurrence must be attributed to the presence of

cytotoxic substances in the urine which, when resorbed. elicit the inflammatory chemotoxic response. It may, however, be possible that they, as well as certain reactions to be described later, contain a chemospecific allergic component (edema, eosinophilia, vascular endothelial granuloma, polypous formation) representing one of the cellular responses of the vesical mucosa upon the contact and resorption of a chemical carcinogen possessing antigenic properties.

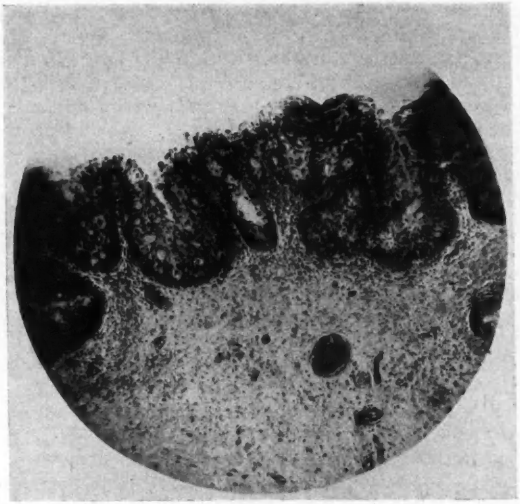


Fig. 2. Leukoplakia with marked epithelial hyperplasia and atypia.

2. *Intra-epithelial abnormalities* were localized pathologic changes in the morphologic character and arrangement of the epithelial cells in the vesical mucosa. They were found in varying number and type in the bladders of the different dogs. In such lesions the epithelial lining is, in many instances thinned, consisting of small pyknotic, ill defined, closely packed, irregularly arranged and occasionally forming indistinctly outlined intra-epithelial nodules. In other instances it is composed of cells with vesicular cytoplasm and small hyperchromatic nuclei (honeycomb type). The irregularity of the cells in size, shape, arrangement and stainability was sometimes so marked that the lesion had the appearance and characteristics of a non-infiltrative carcinomatous coating, similar to that observed in the human uterine cervix. There were also areas made up of small, indistinctly contoured, hyperchromatic cells arranged in numerous short pointed, or tongue-like solid epithelial papillæ. The basal line

of the epithelium, in all the conditions just described, was sharp and straight. There were no vascular or connective tissue changes in the submucosa. In some instances the small, intra-epithelial nodules had partially separated from the epithelial lining and seemed to drop off into the submucosa.

3. *Leukoplakias* consisted of marked mucosal thickenings, composed in the deeper layers of transitional cells and in the more superficial layers of large, polygonal cells. The cells were usually irregular in shape, size and arrangement and often swollen, balloon-like and of signet-ring form. Small intra-epithelial cysts, apparently resulting from localized liquefaction necrosis within the epithelial mucosa and filled with a bluish or pinkish homogenous matter, were often found. Rounded or pointed epithelial pegs, usually, but not always, distinctly outlined and extending into the subepithelial connective tissue, were a characteristic feature (Fig. 2). In some instances the loss of polarity was complete. Large, ill-defined, round or polygonal epithelial cells infiltrated beneath the mucosal lesion in small groups and strands, or as individual cells, penetrating the submucosa and producing the picture of a minute anaplastic carcinoma. In many of the leukoplakias the epithelium was arranged in short, indistinctly demarcated, plump, solid epithelial papillæ, occasionally showing beginning vascularization from the base. The epithelial changes described resembled, in many respects, those seen in the precancerous lesions of other occupational tumors (x-ray dermatosis, arsenical or tar dermatosis). The subepithelial connective tissue was usually edematous and infiltrated with lymphoctyes and leukocytes, which were, at times, predominantly eosinophilic. The capillaries were often dilated and hyperemic in the more advanced stages, which showed also an increased density of the capillary bed. Endothelial granulomas were often present.

4. *Mucous polyps,* which appeared as knob-like mucosal protrusions with narrow pedicles, showed many of the histologic features just described. The epithelial lining of some of these mucosal polyps was composed of an atrophic, thinned, pyknotic or vesicular epithelium, occasionally containing small defects filled with chronic granulation tissue. In other instances the epithelium consisted of from several to many layers of swollen, round-shaped vesicular epithelium with pyknotic nuclei or of a stratified transitional epithelium containing not infrequently complexes of atypical cells, such as hyperchromatic and multinucleated giant cells. In the thickened parts of the epithelial lining there were sometimes small necrotic foci, pseudoglandular cysts and intra-epithelial nodules. A number of the polyps showed small, solid epithelial or fibro-epithelial papillary projections extending from the surface, while others showed epithelial pegs or even diffuse infiltrative epithelial proliferation into the stroma, suggesting early stages of an anaplastic malignant transformation. Lesions of this type usually involved the tips of the polyps.

The stroma consisted of an edematous, loose and, in general, very vascular connective tissue, often infiltrated with lymphocytes and eosinophilic cells. These were not infrequently the main cellular type found in the lumens of newly formed capillaries. The capillary vessels were usually ectatic and varicose. Endothelial granulomas were frequent within the vessels located in the center or near the pedicle. These vascular changes often coexisted with locally corresponding atrophic alterations in the surface epithelium. In many polyps, strands of smooth muscle tissue extended through the pedicles into the cores of the polyps and formed there occasionally, whirl-like, often hyalinized, tufts.

Fig. 3. Benign transitional cell papilloma. The vesical mucosa visible near the papilloma contains a small focus of atypical, closely packed, small epithelial cells.

The neoplastic lesions may be grouped from a pathologic viewpoint as follows:

1. Papilloma with histologically benign structure.
2. Papilloma with histologically benign and malignant component parts.
3. Carcinoma.
   (a) Papillary carcinoma of transitional cell type.
   (b) Nodular infiltrative carcinoma: transitional cell type; pseudoglandular type; anaplastic or sarcomatoid type.

1. *Benign papillomas* were composed by either villous tufts of varying size, composed of slender, delicate, feathery, fibro-epithelial projections, or by rather plump, thick, warty protrusions possessing a larger amount of usually edematous connective tissue in between the epithelial covering. The papilloma may be connected with the wall of the bladder by a very narrow pedicle, or there may be a broader tissue bridge as connecting link, or numerous small papillary

Fig. 4. Pseudoglandular carcinoma, showing a round vesicular type of cells arranged in well defined nests with central liquefaction necroses.

projections (papillomatosis) may extend from the mucosa of the bladder with narrow interspaces. In the thick epithelial lining degenerative changes, such as balloon-like swelling, cytoplasmic vesiculation, nuclear pyknosis, atrophic shrinkage and focal necrosis with pseudoglandular cyst formation were not uncommon features (Fig. 3).

The stroma was a loose and vascular connective tissue with a mild to moderate infiltration of lymphoid and mononuclear cells containing not infrequently an admixture of eosinophilic cells. Brown pigment in the perivascular and subepithelial zones, intracellularly or extracellularly located, was not rare. Hemorrhages into the tip portions were often seen.

2. *Papillomas with benign and malignant component parts* exhibited a general pattern very similar to that just described. But the epithelial lining contained foci of atypical epithelial cells, character-

ized by large cellular and nuclear size, hyperchromatism, irregularity in size, shape and arrangement, increase in mitotic figures and in places by infiltrative growth into the stroma, pedicle and adjacent submucosa of the base. These focal malignant transformations were most frequently located near the pedicle of the papilloma. Small areas of markedly atypical epithelium were often seen in the mucosa of the bladder near the base of papillomas of benign and mixed type.

3. *Carcinomas* were of similar structure as those seen in man and do not need to be described in detail for this reason. There was, however, a tendency toward a pseudoglandular transformation present in these canine bladder cancers, which was much more pronounced than that observed in human aniline tumors (Fig. 4). Neoplasms with true glandular structure have thus far not been seen in the dogs, while they have been occasionally observed in man. None of the carcinomas found in the five dogs which came to autopsy had produced metastases.

The evidence presented justifies the conclusion that the various pathologic lesions observed in the bladders of fourteen out of sixteen dogs were the result of the prolonged exposure to commercial beta-naphthylamine. They are essentially identical in every respect with those found in the bladders of dye workers coming, in the course of their regular work, into contact with certain aromatic amines. The data on hand strongly suggest that the primary and significant action of the carcinogen is exerted upon the epithelium and that the changes occurring in the submucosa, especially the vessels, are secondary and of no fundamental or specific importance for the development of benign and malignant vesical tumors. The histologic evidence obtained shows that there may be severe intraepithelial changes and even infiltrative growth present before any cystoscopically visible manifestations may be demonstrated. While isolated and focal lesions are characteristic of the early part of the manifestation period, a more or less generalized cancerization of the viscus exists during the later stages. The multiplicity of the tumors is a primary phenomenon and is not secondary to submucosal spreading or mucosal implantation. The local distribution of the tumors in the bladder, *i.e.*, their predominance in the dependent parts (dome and anterior surface), is one of the several observations made supporting the concept of a urogenous mechanism of tumor production.

The high incidence of experimental bladder tumors in this series of dogs as well as the appreciable frequency of aniline tumors

among dye workers sufficiently long and intensely exposed to aromatic amines show clearly that these carcinogenic agents are powerful enough to overcome, in the long run, any degree of individual constitutional resistance. This observation, in connection with the fact that aniline tumors are frequently observed in young and middle-aged persons (forty-seven out of eighty-three patients in Evans' series of cases were between twenty to fifty years old), supports strongly the concept that in this occupational cancer the duration and intensity of exposure are the deciding factors and that a normal or pathologic tissue senility (age factor) or an inherited neoplastic predestination have no essential part in their production.

BIBLIOGRAPHY

1. HUEPER, W. C.: "Aniline Tumors" of the bladder. Arch. Pathol. 25:856, 1938; Jour. Indust. Hyg., 16:255, 1934; 18:140, 1936.
2. HUEPER, W. C., WILEY, F., and WOLFE, H. D.: Jour. Indust. Hyg., 20:65, 1938.
3. HUEPER, W. C., BRIGGS, F., and WOLFE, H. D.: Jour. Indust. Hyg., 20:85, 1938.

DISCUSSION

DR. BENJAMIN S. BARRINGER (New York City): I think we are very much indebted to Dr. Hueper for presenting this fine paper today. I should like to ask him just one question, which perhaps isn't fair because it is about the aniline dye tumors in humans. I haven't had the opportunity to observe any of these tumors. In his experience, is there any difference between the aniline dye tumors in humans and the usual run of bladder tumors that we see?

Apparently, he says that a good many of these tumors are anaplastic, perhaps a large portion of them are. That would be rather different from the usual run of bladder tumors that we observe.

The reports from the Wilmington Laboratory apparently indicate that x-ray therapy controls or cures a large proportion of these tumors. If that is so, that will be quite different from what we generally see in the usual bladder tumors. I am wondering if Dr. Hueper has any idea about the differences between these two classes.

DR. WILLIAM E. LOWER (Cleveland, Ohio): There is no question that this organization is deeply indebted to Dr. Hueper for presenting this very classical experimental demonstration. It brings up a number of questions that I should like to ask.

In the first place, I would like to know if there is any evidence that these tumors occur in the upper urinary tract. No report has been given as to whether it occurs anywhere else in the mucous membrane, whether this dye is secreted largely through the urine, or whether it is found in the blood as well. We have long been told that bladder papilloma occur most frequently in aniline dye workers, but here we have a concrete example of an experimental demonstration that it can be reproduced.

I should like to inquire, also, as to whether there is any way of detecting the time at which there is danger of a tumor developing. In other words, what protection does the industrial worker have against the occurrence of such a tumor? What precautions are taken? Is there any time that the probable pre-tumor stage in these cases can be detected?

This, of course, is of very great clinical importance to the industry and to the workers who come in contact with these various dyes. I want to congratulate Doctor Hueper on presenting this very interesting report.

DR. W. C. HUEPER: Spontaneously occurring bladder tumors and those of aromatic amine origin are grossly and microscopically identical.

DR. BARRINGER: When they have become carcinomatous, are the larger proportion of them anaplastic?

DR. HUEPER: No, I would not say so from my present experience, which is mainly gained from the detailed histologic study of diffusely involved bladders. The wall of the bladders was cut into strips 3 to 5 cm. long. The most striking feature observed at the examination of sections prepared from them was not so much the occurrence of highly anaplastic lesions as the coexistence of morphologically markedly different lesions in the same section and various sections of the same bladder. The diversity of epithelial pathologic lesions in a strip of vesical mucosa, 5 cm. long, was sometimes remarkable.

With the exception of a few of the very early intra-epithelial changes found in the bladders of these dogs identical preneoplastic and neoplastic lesions have been observed in the bladders of aniline dye workers. While none of the dogs which came to autopsy have shown any metastases, localized neoplastic penetration of the entire wall of the bladder existed in one instance, in which tumorous masses had narrowed the vesical lumen to the extent of a narrow canal.

It is interesting in this connection to note that the reports from different countries as to the malignancy of aniline tumors vary considerably. Simon, in Germany, considers aniline tumors as relatively benign, as he has a high proportion of cures and almost never in his fatal cases any metastatic spread. But a few miles farther south, in Switzerland, Mueller is emphatic in stating that these occupational neoplasms, according to his observations, are highly malignant, that they have an unfavorable prognosis and produce not infrequently metastases not only in the regionary lymph nodes, but also in remote organs.

While the therapeutic results obtained in the United States seem for the time being to agree with those reported by Simon, it seems to be uncertain whether these favorable arrests of aniline tumors are actually permanent. Serious doubts must be entertained in this respect for two reasons. As dye workers with aniline tumors of the bladder are in this country returned to their hazardous work when the clinical condition permits a continuation in their previous occupation, the bladder mucosa of these men, which according to all experience with this and other types of occupational tumors must be considered as predisposed and sensitized, is again exposed to the carcinogenic agent and will therefore react much more readily and quickly to this stimulus than a normal mucosa. Recurrences or, more correctly, new primary tumors must be expected under such circumstances. The prospects of a permanent cure are doubtlessly greatly decreased in the individual case under these conditions.

The second observation which seems to support such a conception may possibly be represented by the occurrence of a second primary tumor in another organ in addition to that of the bladder in three out of six cases which came to autopsy in this country. In one instance there was a carcinoma of the renal pelvis with metastases; in a second case a primary carcinoma of the pancreas was found and in a third case a primary carcinoma of the skin was observed. While this may represent merely a peculiar coincidence, it may on the other hand be possible that the intensity of exposure to a carcinogenic agent may have played a rôle.

The medical control of the disease is best accomplished by periodic cystoscopic examination of the exposed workers if the cooperation of the workers can be obtained in this regard. The early recognition and proper treatment of the bladder lesions, if possible during the preneoplastic stage, is the best medical management. But, as already mentioned, even this will be effective only if the worker is permanently removed from any further contact with the carcinogenic material. Experience has shown that it is difficult to induce the dye workers to submit to such examinations. They are not routinely performed in German and Swiss dye works for this reason, and are also in this country only partially in effect.

It is, therefore, obvious that the effective control of this disease of an industrial origin cannot be accomplished when the damage is

done, but must rely upon the elimination or marked reduction of the occupational contact with the carcinogenic substances. The introduction of completely closed production systems in the dye industry, the installation of exhaust ventilation, prevention of dust, cleanliness of the work rooms and personal hygiene of the workers are much more important than the most skilled and competent medical care of dye workers with well manifested bladder lesions.

Engel, in Germany, and my former collaborator, Wiley, have demonstrated that beta-naphthylamine is excreted in the urine in the form of an ethereal sulfate of 2.1 aminonaphthol. There are probably other metabolites. But at the present time it is still uncertain which one or how many of them are carcinogenic. It is rather unlikely from the evidence so far available that the beta-naphthylamine as such has carcinogenic properties.

PRESIDENT RANDALL: Dr. Hueper, may I extend to you the thanks of the Association in appreciation of your work and congratulate you for it.

ENDOMETRIOSIS OF THE URINARY BLADDER

J. C. McCLELLAND, F.R.C.S.(C)

Toronto, Ontario, Canada

Endometriosis is looked upon as a condition which lies entirely within the field of the gynecologist, but at times the general surgeon and the urologist may be called upon to deal with it. The first case was reported by Judd in 1921. Since then Mark has collected thirty-four cases from the literature. In only three of these was no evidence of the lesion found in the peritoneum or the vesico-vaginal fold.

ETIOLOGY

Most cases of endometriosis follow some form of pelvic operation on the female organs. The symptoms are cyclic in occurrence, coming immediately before and during each menstruation. There is usually pain over the bladder area, frequency and pain at the end of urination. Hematuria has not been a symptom, but microscopic blood is found in the urine during the period.

The cystoscopic picture varies from a localized reddening of the mucosa to a bluish form of cysts. These cysts are in a puckered area of the bladder and covered by the mucosa. During the intermenstrual periods there is a decrease in the size of the mass.

Treatment is directed to the removal of the ovarian hormonal influence. Sterilizing doses of x-ray or surgical removal of the ovaries causes a disappearance of these symptoms.

REPORT OF CASE

Mrs. M. G., aged forty-one, was seen September 25, 1937.

First Visit.—This patient was seen first in January, 1930, when she complained of a boring pain in the right flank which radiated up the back and down into the right hip. She also complained of tenderness low over the bladder in the mid-line.

Four months previously she had had a cesarean section for a three months' pregnancy, with ligation of the fallopian tubes.

She had a frequency of twice each night, and every two hours in the daytime; also, a slight burning on urination.

Complete cystoscopy with urograms resulted in negative findings and it was thought she was suffering from a visceroptosis or ureteral

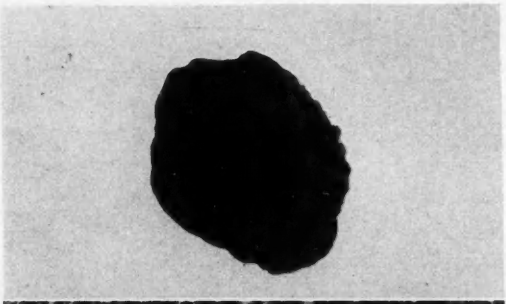


Fig. 1 *(above)*. Photograph of partial resection specimen from bladder showing area of endometriosis in the section.

Fig. 2 *(below)*. Photomicrograph of endometriosis removed from outer wall of the bladder under the cyst-like body shown in Figure 1.

stricture. Dilatation of the ureter and abdominal supports did not relieve her symptoms. The urine was negative on culture and microscopically.

Second Visit (January 18, 1934).—She complained of a dull aching pain in the right lower quadrant, also some frequency. The lower abdomen showed a very slight tenderness and the kidneys were not palpable. Pelvic examination was negative, as also was the examination of the urine.

Cystoscopy was carried out without ureteral catheterization and the following observation was made: "On the right posterior part of the bladder behind and above the right ureteral orifice, was an area of redness about the size of a fifty cent piece. This was a definite area and seemed to me to be due to some adhesion to the bladder from the inside of the abdomen."

Third Visit (September 25, 1937).—She complained of a good deal of pain at the end of urination which was worse during menstruation, referred into the right lower quadrant. She also had irregular menstruation and wondered if her menopause was approaching. No hematuria was present and the urine showed no blood. It was not examined during menstruation.

Vaginal examination showed a small lump the size of a walnut, felt to the right of the body of the uterus, thought to be in the broad ligament or attached to the body of the uterus.

Cystoscopy.—The urethra was quite small. On the right posterior wall was an area of puckering containing two blue cyst-like areas. This corresponded to the area of the mass felt on vaginal examination.

The patient was referred to Dr. W. W. Lailey, who had seen her and operated on her seven years before. After consultation, we recommended operation to explore the abdomen to determine whether any endometriosis was present and, if so, to remove the ovaries to allow it to subside.

Operation.—This was carried out jointly with Dr. Lailey. A midline incision immediately above the pubis was made and the abdomen explored. The uterus and ovaries were involved in a great many adhesions, but no evidence of endometriosis was found. The mass felt on vaginal examination was within the bladder wall and independent of the pelvic female organs. As no evidence of endometriosis was seen grossly in the peritoneal cavity, I considered seriously that the lump in the bladder wall must be a carcinoma. Accordingly, after the uterus and ovaries had been removed by Dr. Lailey, the peritoneum was separated from the back of the bladder wall and the lump was resected extraperitoneally. A puncture wound was made in the vertex of the bladder and a de Pezzer catheter drawn

through to the lower end of the incision. The opening in the bladder where the resection was done was closed.

The patient made a very good recovery and was completely free of her bladder symptoms.

Pathologic Report (Dr. W. L. Robinson).—Diagnosis—Endometriosis of the urinary bladder; glandular hyperplasia of uterus; peritoneal adhesions.

The body of the uterus, which measured 5.5 x 5.0 x 4.5 cm., had been removed as a sub-total hysterectomy and the outer surface, with a shaggy appearance, was covered by numerous fibrous tissue adhesions. On palpation it was firm in consistency with occasional small nodules palpable in the uterine wall. On making gross serial sections of the body these were seen to be of very small size, greyish white in color with interlacing whorls of tissue. On opening into the uterine cavity, it was found to measure 3 x 5 cm. in length from the point of resection to the fundus and was lined by a soft, redundant, yellowish-grey mucosa. It was almost in direct apposition to the serosa. In the fundic portion no resistance whatsoever was encountered in putting a snap through the wall of the uterus in this situation.

The right fallopian tube, measuring 7.5 x 0.8 cm. was pinkish grey and slightly tortuous. The fimbriated end lay free and the tube could be readily probed for a short distance. The right ovary, measuring 3.5 x 2.2 x 1.5 cm., was yellowish grey in color, though mottled by dark reddish purple, patchy areas of hemorrhage. On section it contained one cyst filled with dark red blood, which measured 1.8 cm. in diameter and was lined by yellow lutein tissue. Numerous small lutein bodies were present on the cut surface of this ovary.

The left fallopian tube, measuring 7 x 0.7 cm., was purplish grey in color. The fimbriated end lay free and it could be probed for a short distance. The ovary on this side was essentially the same in appearance as that encountered on the right side. Numerous adhesions covered the surfaces of the tubes and ovaries on both sides so that the specimen, as a whole, had rather a shaggy appearance.

The tumor from the bladder wall, which measured 3.5 x 3.0 x 2.5 cm., consisted of a firm nodule of tissue, one surface of which was blue in color, smooth and glistening, and from a central position there projected a hemorrhagic, soft nodule which measured 1 x 0.8 x 0.8 cm.

Sections taken through the tumor in the bladder wall showed an endometrial infiltration of the whole wall, made up of glands and stroma similar to endometrial tissue.

Section of the uterus showed a fairly marked hyperplasia of the glands of the endometrium. There were a number of peritoneal adhesions on the surface of the uterus. Some of them had little hemorrhages into them, but there was no evidence of endometrial implants.

COMMENT

This patient had had a pelvic operation which was followed immediately by bladder symptoms. No lesion was seen inside the bladder until her cystoscopy four years later when an area of localized redness was noted. Later the bluish cyst-like bodies were seen in the area which had localized redness three years before. Apparently the redness was the evidence of the endometrial invasion in that portion of the bladder wall.

The absence of endometrial tissue in the peritoneal cavity led to a change of diagnosis during the operation and to a resection of the localized lump in the bladder. If endometrial implants had been found the oöphorectomy would have been sufficient and resection would not have been done.

NEW METHODS OF IRRADIATING BLADDER TUMORS

ARCHIE L. DEAN, M.B.

New York City

I apologize to this clinical group for presenting material in such an experimental phase. However, the results of treating bladder cancers with any of the approved methods are so disappointing that promising new procedures should be studied. The purpose of this paper, therefore, is to describe two methods of irradiating bladder tumors which are on clinical trial, although neither has been perfected. From the standpoint of physical computation the methods should be of practical value.

While interstitial irradiation with gold radon seeds and external irradiation with high voltage roentgen rays are the most efficient methods at present of applying radiation to bladder tumors, each procedure has inherent disadvantages. When gold seeds are used it is impossible to obtain an even distribution of radiation. Close to each implant the irradiation is much greater than a short distance away. Because it is necessary to give at least the minimal curative dose to all parts of the tumor with a certain number of separate sources, those portions close to implants must receive considerably more than the minimal dose. For this reason and the fact that in practice the sources can hardly be distributed uniformly throughout the tumor, the total dose administered is far in excess of the required minimum, assuming an ideal distribution. In clinical practice this factor is of little importance when tumors are of moderate size, but if the growths are large a devitalizing dose of interstitial radiation may be seriously destructive to adjoining tissues.

On the other hand, high voltage roentgen ray units used at the usual distances of 70 to 100 centimeters, provide a reasonably even distribution of the rays to all parts of the tumor. However, so little of the radiation reaches the deeply situated bladder tumor that it is impossible to deliver a curative dose without seriously damaging the intervening tissues, especially as the majority of these tumors are radioresistant.

It has long been recognized as highly desirable to make use of

Fig. 1 *(above)*. The cone fitted in the suprapubic opening with the tumor centered in the distal end.

Fig. 2 *(below)*. The portable unit has been attached to the cone and radiation is being administered.

the ideal radiation distribution obtained by applying the roentgen rays directly to the bladder tumor, but no suitable apparatus has been available. Recent developments in the design of roentgen ray tubes suggest that before long it will be possible to give a successful therapeutic dose of roentgen rays to bladder tumors at a single application. Direct irradiation of a bladder tumor through a suprapubic opening is not an original conception of the writer. He regards this form of treatment advantageous only if the tumor can be cured by a single exposure.

Probably the crudest method of this type is one which has been used on three patients in which a 60 kilovolt portable roentgen-ray unit has been employed. The patient is prepared as for any other suprapubic operation. Surgical asepsis is observed without unusual difficulty and spinal anesthesia is satisfactory. The bladder is opened suprapubically and the tumor exposed. If the growth is papillary the intravesical projection is removed with a cautery snare. This is unnecessary if the tumor is of the flat, infiltrating type. An aluminum cone 5 centimeters in diameter is fitted in the bladder so that the tumor is in the center of the distal end. The cone is then attached to the roentgen-ray unit and radiation is applied.

About three years ago Chaoul designed a roentgen-ray tube in which the target is at one end and at ground potential. With this tube the target itself can be inserted in body orifices such as the mouth or rectum, and by the use of cones of different sizes and shapes roentgen rays can be directly applied to tumors of these regions. In the same way bladder tumors can be treated through suprapubic incisions.

The curative dose of roentgen rays directly applied to a bladder tumor in one treatment is not known. Since such a dose can be recognized only by the biologic reaction it produces, and because animal experiments are of little, if any, value in predicting these reactions on the human bladder, one must proceed cautiously while carefully observing the reactions of different doses on cancer patients.

Clinical research on radiation dosage, reported in 1935, suggested that the average successful dose of interstitial radiation for treating bladder tumors was about 10 to 12 threshold erythema doses (T.E.D.). In attempting to determine the equivalent dose

of roentgen rays, one must take into account two important factors: (1) The radon seed treatment continues at a diminishing rate for a considerable time, whereas the roentgen-ray treatment through a suprapubic opening is preferably given in one sitting. No data are available to translate the biologic effectiveness in bladder tumors of the long continuous treatment into a short treatment, but as a first approximation one may take a factor of two.

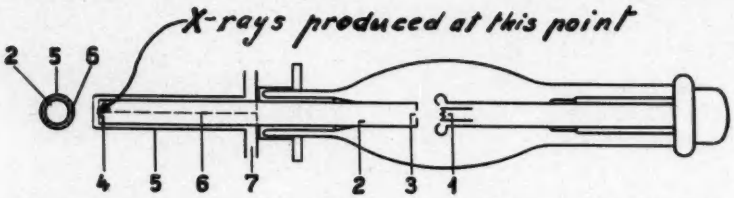


Fig. 3. Diagram of section of the tube. (1) Hot cathode. (2) Anode. (3) Entrance window for cathode rays. (4) Window of copper sheet 0.3 mm. thick. (5) Cooling cover. (6) Water circulation guide. (7) Connection for cooling water lead.

That is, it may be assumed that one-half the dose of the long treatment will be just as effective if given in a short time (of one hour or so). (2) The erythema dose in terms of roentgens varies considerably with the quality of the radiation used, being approximately 300 r for low voltage roentgen rays and about 1,500 r for gamma rays. It is not known whether bladder tumors differ in sensitivity with respect to quality of radiation in the same way that the human skin does, but it is unlikely that such is the case. In the absence of definite information it is safer to assume that doses of equal roentgen values are more nearly biologically equivalent in the tumor.

Ten T.E.D. of gamma radiation represent a dose of about 15,000 r. Because of the excessive radiation administered when gold seeds are used due to uneven distribution, a factor of 2 should be used. This reduces the 15,000 r to 7,500 r. Again, the effective period of gold seed irradiation is about six days while that from the 60 kilovolt unit is of the order of one or two hours. This, as just mentioned, also requires correction by an approximate factor of 2, which reduces the required successful dosage to 3,750 r. Because infiltrating tumors are often 1 centimeter thick, the problem is to determine how great a surface dose must be given with the

60 volt portable unit and the Chaoul unit to deliver 3,750 r to a depth of 1 centimeter and what the duration of such a treatment will be.

The portable unit employed has no metallic filter, but the immersing oil acts as a filter and the quality of the emergent radiation corresponds to half-value layer of 0.9 millimeter of aluminum. At a distance of 27 centimeters with a 60 kilovolt peak at 5 milliamperes of current, 50 r per minute reach the surface of the tumor and the following depth doses are delivered:

Depth	Surface dose received
1 centimeter	61 per cent
2 centimeters	46 per cent
3 centimeters	34 per cent

The Chaoul unit operates at 60 kilovolts and embodies a filter of 0.2 to 0.25 millimeters of copper. The half-value layer of the radiation is 3.3 millimeters of alumnium. At 5 centimeters distance the surface dose is about 90 r per minute and the depth doses are:

Depth	Surface dose received
1 centimeter	70 per cent
2 centimeters	45 per cent
3 centimeters	30 per cent

Using these factors it can be computed that to administer 3,750 r to a depth of 1 centimeter with the portable unit a surface dose of 6,250 r must be given. The duration of this treatment is 125 minutes.

With the Chaoul unit to deliver 3,750 r to a depth of 1 centimeter a surface dose of 5,400 r must be given. This requires 60 minutes.

Both figures are, of course, only approximations to be used as a guide. To minimize the risk of over-treatment the first patients were given about one-half of this amount.

Comparing these figures, it is evident that the Chaoul unit is more convenient to use. On the other hand, because of the greater distance of the portable tube there is a more even distribution of radiation. Which unit will be found more useful therapeutically only clinical trial will determine.

In addition to the units described, another has been manufactured and is now in experimental use. How it will compare can not as yet be known. Finally, a fourth tube has been designed similar to the Chaoul which will be modified with the purpose of greatly increasing its output.

SUPER-VOLTAGE RADIATION IN THE TREATMENT OF BLADDER TUMORS

FLETCHER H. COLBY, M.D.

From the Huntington Memorial Hospital, Boston, Massachusetts

A million volt x-ray generator for the treatment of malignant disease was installed one year ago in Boston, at the Huntington Memorial Hospital. This unit was designed and constructed by Dr. R. J. Van de Graaff and Dr. J. G. Trump of the Massachusetts Institute of Technology and is operated under the direction of Dr. Richard Dresser.

The high voltage source is a direct current electrostatic generator of the belt type. This is essentially a belt conveyor of electricity, electric charge being transferred between a high voltage terminal and ground at a uniform rate by six commercial, four-ply fabric belts. The belts are each three feet wide and travel between the lower grounded pulleys and corresponding pulleys twelve feet above within the high voltage terminal. The belts run at a speed of from 4,000 to 5,000 feet a minute, the ascending belts carry negative charge to the high voltage terminal, and the descending belts carry away positive charge. Exceedingly high voltages are built up by this method.

The generator is unique in design and operates at a constant potential with an effective voltage of over 1,000,000 volts, and can deliver 3 milliamperes of current on the x-ray target at this voltage. In principle it differs from other treatment units.[3]

Eight instances of malignant disease of the bladder treated by this machine are reported. These are less than half the number of similar cases so treated, since others are private patients with insufficient data or too recent to be of value.

Super-voltage treatment of malignant disease may represent an advance over former methods of lower voltage x-radiation, although we cannot yet evaluate its efficiency. Favorable effects from its use, as with other forms of deep therapy, in causing tumor regression have been evident. Likewise, disappointments have been encountered in tumors which seem to be "radio-resistant." Treatments have been cautiously given without an adequate knowl-

edge of dosage or ultimate effects. Patients seem to tolerate this high voltage and short wave length, with less general reaction, x-ray sickness and skin change than with lower voltages. Screening sufficient to cut out the rays delivered by the 200 kilovolt machine eliminates the destructive effect of the longer waves, so that larger doses with deeper penetration are employed without untoward results. Many individuals of advanced years in deplorable general condition have tolerated these super-voltage treatments surprisingly well, symptoms have abated and impaired health has improved.

Before starting such treatment in bladder malignancy each individual is given preliminary study. General physical examination, blood studies, renal function tests and cystoscopic examination are routine. In so far as possible, portions of the tumor are removed before treatment and studied histologically. The difficulties of frequent biopsy are readily understood, but we attempt to follow the progress of tumors under treatment by frequent cystoscopic examination and biopsy at different stages in the course of treatment.

Histologic changes in radiated tissues are receiving increasing attention. In carcinoma of the cervix they form a basis for the administration of radiation. The less accessible bladder tumors render similar study more difficult, but with more time and material such work may prove valuable. The protective processes of the body cause changes in certain malignant tumors which are easily mistaken for radiation effects, such as an increase in connective tissue, vacuolization, hyalinization, blood vessel and nuclear change. Only uniform methods of preservation, fixation and tissue staining are of value. It is obviously unfair to compare the shrunken cell structure of specimens rapidly fixed for celloidin preparations with that of the more carefully preserved Zenker fixed tissues, imbedded in paraffin. The delicate changes of the nucleolus, mitochondria and Golgi apparatus, recently described by Colwell,[1] Fogg and Warren,[2] and others, demand special preservation, careful staining and meticulous technic. The importance of such changes in cell structure as applied to radiated bladder tumors is unknown.

This is the present plan adopted for the treatment of bladder tumors:

A daily dose of 400 r units through three alternating portals, anterior pelvis, posterior left and posterior right. Size of portals, 10 x 10 cm. or 12 x 12 cm. Exposure time, 5 minutes 45 seconds, 1.2 milliamperes of current. Filtration, 5 mm. of lead. Half value layer of copper 11 mm. Focal skin distance 70 cm.

We consider wide surgical excision the most suitable treatment

Fig. 1. Case 1. Intravenous pyelogram, June 28, 1937, before super-voltage radiation, irregular filling defect of bladder suggestive of tumor.

of bladder malignancy and when possible circumscribed growths are removed by operation. Super-voltage radiation is advised only when the extent of the tumor renders operation impractical or other factors make surgery unwise. For the most part debilitated individuals with extensive disease are radiated.

Some of our problems and results are illustrated by the following cases:

Case 1.—W. MacA., aged forty-seven. Huntington Memorial Hospital, July 29, 1937.

The patient's first gross hematuria occurred three years ago. His

SUMMARY OF CASES

Case	Description of Tumor	Previous Treatment	Super-voltage (1,000,000 Volts) Radiation r Units	Result
1. W. MacA. 47 yrs. No. 37-986	Papillary carcinoma filling lower third of bladder. Not infiltrating.	None	Aug. 10-Sept. 30 1937 13,200	Marked regression. Cell vacuolization and autolysis.
2. J. F. 73 yrs. No. 37-936	Huge papillary growth bladder neck and right wall.	None	July 19-Aug. 3 1937 5,600	Marked regression. Contracted bladder. No visible tumor.
3. H. F. 73 yrs. No. 37-621	Epidermoid carcinoma. Rapidly growing infiltrating growth left lateral wall	None	May 18, '37-Feb. 7, '38 16,800	Marked intravesical regression. Persistent deep induration.
4. G. T. 78 yrs. No. 38-76	Epidermoid carcinoma highly malignant. Sessile growth, left base and lateral wall.	None	Jan. 21-Feb. 8 1938 6,000	Considerable intravesical regression. Persistent large extravesical mass.
5. R. E. 82 yrs. No. 37-1065	Papillary carcinoma recurrent, rapidly growing. Multiple tumors	Fulguration 12 yrs. ago. Open operation 2 yrs. ago.	Aug. 19-Nov. 10 1937 12,000	Some intravesical regression, but little benefit. Persistent pain.
6. W. B. 48 yrs. No. 37-949	Epidermoid carcinoma recurrent, extensive and very malignant.	Electro-coagulation Permanent cystotomy. X-radiation.	July 20-Oct. 9 1937 8,400	No evident effect. Persistent symptoms.
7. F. S. B. 83 yrs. No. 37-1169	Papillary carcinoma recurrent, extensive. Bladder neck and walls.	Electro-coagulation. Permanent cystotomy	Sept. 7-Oct. 3 1937 6,000	No evident effect. Persistent pain.
8. J. McE. 73 yrs. No. 38-279	Epidermoid carcinoma extensive, infiltrating. Bladder base.	None	Mar. 21, 1938 Apr. 7, 1938 6,000	Symptoms relieved. Local effect unknown. Apparent regression.

physician administered medicine and no further bleeding was noticed until nine weeks before entering the hospital. During this interval a considerable amount of blood was passed in the urine and the patient was referred to a urologist for adequate examination. The bladder was examined on July 27, 1937, by Dr. H. H. Crabtree, who found that papillary tumor surrounding the bladder outlet obliterated an adequate view of most of the interior. The lateral walls were not visible,

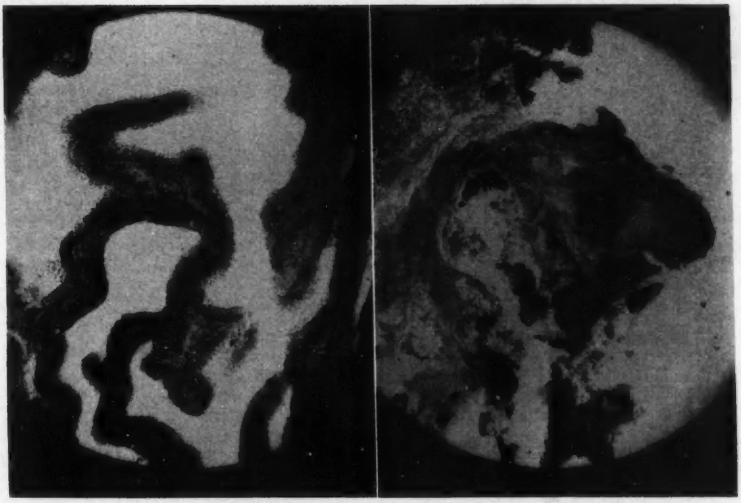


Fig. 2. *(left)* Case 1. Low power of tumor Sept. 16, 1937, during the early stages of super-voltage radiation. Extensive papillary carcinoma of bladder.

Fig. 3. *(right)* Case 1. Low power of section of tumor after about 10,000 r units of super-voltage radiation. Marked necrosis of tumor tissue and cell autolysis.

but that portion of the back wall which could be seen was covered with rough, gray slough. A normal upper urinary tract was demonstrated by intravenous pyelograms (Fig. 1), with an irregular defect in the bladder region suggestive of tumor. Since the new growth appeared extensive, as radical a measure as total cystectomy was seriously considered.

The patient was admitted to the hospital on July 29, 1937, and examination confirmed Dr. Crabtree's estimate of the situation. The lower third of the bladder was covered with patchy, white slough, the outlet surrounded by pale, papillary tumor. A soft bladder base gave no evidence of tumor infiltration into the deeper tissues. The patient's general condition was somewhat impaired by continued bleed-

Fig. 4. Case 1. Appearance of tumor 3 months after 13,200 r units of super-voltage radiation with marked tumor regression. Low power. Note vacuolization of tumor cells.

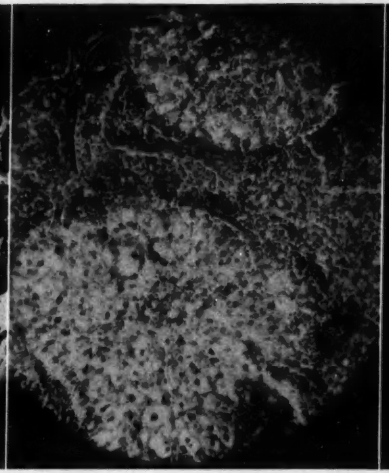


Fig. 5. Case 1. High power of tumor after super-voltage radiation. Vacuolization of tumors cells with shrunken deep staining nuclei.

Fig. 6. Case 1. Cystogram Dec. 10, 1937, six months after Figure 1, showing well filled, normal bladder of good capacity. About two months after 13,200 r units of super-voltage radiation.

ing but, except for the anemia, a red blood count of 3.5 million and hemoglobin of 59 per cent, he appeared well. Super-voltage radiation was started August 10, 1937, with a daily dose of 400 r units through three fields, one anterior and two oblique, portals 10 x 10 cm. By August 31, 1937, 7,200 r units were given. On September 17, 1937, bleeding had almost ceased, his general condition had improved, lost weight had been recovered; the red blood count had risen to 5.3, and the hemoglobin to 98 per cent. Several good sized pieces of necrotic tissue had been voided.

From September 14 to 30, he received an additional 6,000 r units, making the total 13,200 r units. There was some erythema over the suprapubic region, but there was no great skin reaction. He looked and felt well. September 16 the bladder contained long fringes of tumor about the outlet and dead-white necrotic tissue in the interior.

Biopsy Report: "Long narrow papillæ consisting of well defined transitional epithelium, supported on a narrow stroma of fibrous tissue containing some dilated blood vessels. No mitoses seen. Slight lymphocytic infiltration" (Fig. 2).

Tissue from the bladder on September 20, consisted of only calcified and necrotic material with chronic inflammation (Fig. 3). Three weeks later, October 21, fringes of papillary tumor were present at the bladder neck, but the tumor mass was evidently considerably smaller. Two months later, December 23, the only signs of neoplasm visible in the patient's bladder were four or five very small, papillary outcroppings on the bladder base. Each one was less than 1 cm. in diameter and all were easily removed by transurethral operation. This tissue contained actively growing tumor cells with fibrosis of the blood vessels and vacuolization of many of the tumor cells (Figs. 4-6). The patient felt perfectly well. On February 8, 1938, no tumor could be seen in the bladder and except for small, localized, edematous areas above each ureteral orifice the mucous membrane appeared normal.

Comment.—The patient was a robust man with extensive involvement of the bladder by a superficial tumor of low malignancy. Administration of 13,200 r units of super-voltage radiation caused considerable regression of the neoplasm. There were no marked general reactions or excessive skin changes in spite of massive x-radiation. Here, a situation so serious that total cystectomy was under consideration was reduced to simple terms with a fair possibility of eventual cure.

Case 2.—J. F., aged seventy-three. Huntington Memorial Hospital, July 15, 1937.

This patient, a frail, cachectic man, came to the Massachusetts General Hospital three and one-half years ago. Although hematuria

was copious at that time and cystoscopic examination was urged, he disappeared until June 8, 1937. A considerable degree of weakness and dyspnea were attributed to continual loss of blood, the red blood count being 2.4 and hemoglobin 45 per cent. A huge, papillary growth surrounded the bladder outlet which extended up the right lateral wall. Normal kidneys and ureters were demonstrated by intravenous dye with a large filling defect of the bladder (Fig. 7).

Fig. 7. *(left)* Case 2. Extensive papillary tumor of bladder. Cystogram June 16, 1937, before super-voltage radiation.

Fig. 8. *(right)* Case 2. Cystogram one month after completing 5,600 r units of super-voltage radiation. Small contracted bladder with incompetent ureteral orifices. The filling defect probably represents persistent tumor. Compare with Figure 7.

An obviously poor subject for any form of treatment, the patient was given a blood transfusion and sent to the Huntington Memorial Hospital for x-ray treatment. In spite of the duration of symptoms, poor general condition and unhealthy appearance, there was no real evidence of the spread of malignant disease beyond the bladder itself, although soft induration of the bladder base was felt above the prostate.

From July 19 to August 3, 400 r units of super-voltage radiation were given daily. On August 10, bleeding had stopped and he appeared to be doing well. About a month later, September 2, 1937, he had lost weight and did not look well. However, there was considerable change in the appearance of the bladder (Fig. 8). The bladder mucous membrane was reddened throughout, but the only visible sign of tumor was a small, ulcerated area 2 cm. in diameter on the right lateral wall, above the trigone, covered with white slough. A raised, roughened ridge of tissue 2.5 cm. in length and 1 cm. wide, not papillary in character, extended from this point along the lateral wall of the bladder. This was considered to represent solid neoplasm. Bladder irritability was considerable and its capacity less than 1

ounce. The situation at this time is well illustrated by the cystogram.

On October 14, about two and one-half months after the last x-ray treatment, the patient was exceedingly uncomfortable from bladder discomfort and frequent urination. The cystoscopic picture was unchanged. Anemia was less of a feature, the red blood count being 3.5, hemoglobin 60 per cent. On March 10, 1938, his general appearance was considerably better, but the bladder capacity was about a tablespoonful. The mucous membrane was less reddened, no sloughing tissue was present, and nothing resembling tumor was seen through the cystoscope or felt on rectal examination. There had been no radiation or marked skin change.

Comment.—This is a case of marked tumor regression from super-voltage radiation, in an exceedingly run-down, elderly man. It was felt that a moderately large dose of super-voltage x-radiation was tolerated with less reaction than is customary with lower voltages. Administration of 5,600 r units, however, resulted in considerable bladder contraction along with the astonishing change in the tumor.

Case 3.—H. F., aged seventy-three. Huntington Memorial Hospital, May 6, 1937.

The patient was an obese man of good appearance, with bladder irritability during the past year, whose first hematuria was but two weeks ago. A shaggy, necrotic growth covered the whole left lateral wall of a bladder with very small capacity. Tumor infiltration, through the bladder wall, above the prostate, with probable extension posteriorly to the wall of the pelvis, was readily appreciated by rectal examination. His general condition being good, large doses of deep radiation were planned. From May 18 to June 2, 1937, 400 r units were given daily, a total of 5,200 r units. On June 3, 1937, considerable regression of the tumor was apparent. A rough granular area was present high up on the left of the bladder base and a small, papillary growth projected between this and the bladder neck. The mass previously encountered on rectal examination was no longer felt. No discomfort from the treatments was experienced by the patient, but the bladder felt worse. One week later, June 10, through the cystoscope, were seen the pallid remains of the tumor which had shrunk to an area no larger than 2 cm. No other tumor was visible but the induration of the left of the bladder base was as large as before treatment. About three weeks later the bladder had become so much better that the patient was able to go three hours without voiding. Now the only sign of tumor was a granular area to the left of the trigone in a less congested and elsewhere normal bladder.

From June 21 to 26, an additional 2,800 r units were given in daily doses of 400 r units accompanied by some nausea. On July 8, no

definite tumor was visible in the bladder, but a shaggy area on the left ureteral ridge persisted. Two months later, September 8, the bladder presented much the same appearance except that the area before mentioned resembled more closely actively growing tumor and the same induration was felt rectally. A biopsy of the intravesical lesion contained actively growing, healthy tumor, epidermoid carcinoma (Fig. 9). In view of this report, 2,400 r units were given

Fig. 9. Case 3. Infiltrating bladder tumor, epidermoid carcinoma. Low power of tissue removed Sept. 8, 1937, after 8,000 r units of super-voltage radiation. Despite tumor recession, actively growing cancer is present.

Fig. 10. Case 3. Cystogram about 2 months after 16,800 r units of super-voltage radiation. Bladder of good capacity. No symptoms. Persistent infiltrating tumor.

from October 4 to October 9, 1937. On October 28, examination of the bladder still showed a small, raised area around the left ureteral orifice. From October 29 to November 4, 2,400 r units brought the total radiation to 12,800 r units. There had been no marked general reaction and only bronzing of the skin above the pubes. On examination, December 2, there was still a raised, edematous area around the left ureteral orifice with hard infiltration in this region on rectal examination. From February 7 to 16, 1938, 400 r units were given daily without further reaction.

When last examined, April 7, 1938, eleven months after the first treatment, this patient had received super-voltage radiation which totalled 16,800 r units His general appearance was good, and bladder discomfort was absent. Surrounding the left ureteral orifice the

same persistent edema was observed and the same degree of thickening was felt through the rectum. Healthy appearing tumor was present again in a biopsy from this area. Some dilatation of the left kidney pelvis and upper third of the ureter are evident in a recent intravenous pyelogram. The skin of the suprapubic region was well tanned but very slightly thickened (Fig. 10).

Comment.—This is a case of infiltrating malignant tumor in the bladder of an elderly but well-conditioned individual, who tolerated

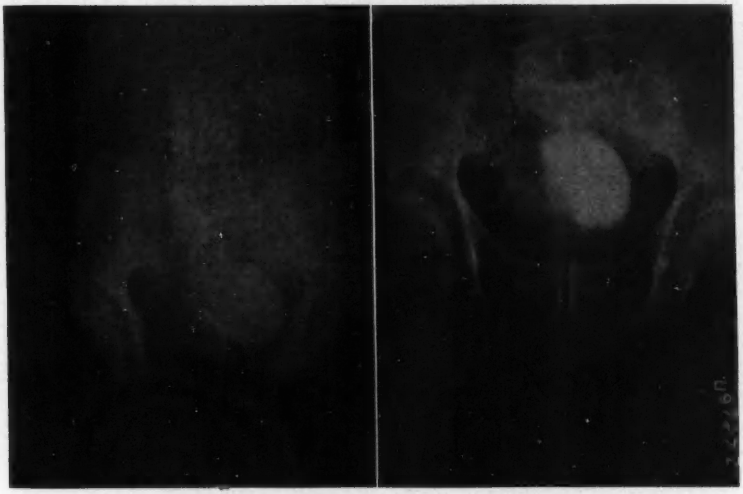


Fig. 11. *(left)* Case 4. Epidermoid carcinoma of bladder. Extensive filling defect of left side of bladder, before radiation.

Fig. 12. *(right)* Case 4. Cystogram after 6,000 r units of super-voltage radiation. Although the tumor had regressed from the cystoscopic appearance there has been little change in the cystogram. A large plaque of infiltrating tumor was present at post-mortem examination.

16,800 r units of super-voltage radiation without untoward results. X-radiation appeared to result in considerable regression of the intravesical portion of his tumor but malignant infiltration in the deeper structures persisted.

Case 4.—G. T., aged seventy-eight. Huntington Memorial Hospital, January 20, 1938.

Symptoms for two years, difficult urination, pain and occasional bleeding, were the complaints in this case. Except for mild anginal attacks the patient had been well. Senile cataracts were added evi-

dence of arterial change. A cardiac consultant reported advanced arteriosclerosis with coronary heart disease, angina pectoris and narrow margin of reserve. A considerable degree of benign enlargement of the prostate and impaired renal function accompanied an extensive malignant tumor of the bladder. He had moderate anemia, red blood count 3.3, hemoglobin 60 per cent. Blood pressure was 150/90. The left of the bladder base was covered by a solid, sessile,

Fig. 13. Case 4. Highly malignant rapidly growing tumor, epidermoid carcinoma Grade III. There was little change evident in this neoplasm after 6,000 r units of super-voltage radiation. Low power.

infiltrating tumor which arose above the ureteral opening, and spread outward and upward as far as the anterior wall. Most of the growth was covered with gray slough. Tumor invasion of the bladder wall was evident rectally. Tissue removed was epidermoid carcinoma, Grade III (Fig. 13). Cystogram: Gross irregular filling defect of the greater portion of the left side of the bladder (Fig. 11).

From January 21 to February 8, 1938, the patient received 400 r units of super-voltage radiation daily. Upon the completion of 6,000 r units complete urinary retention necessitated transurethral resection

of the obstructing prostate. An opportunity was thus afforded to study the effect of the radiation upon the bladder tumor. Considerable change in the intravesical portion of the new growth was apparent. On February 18, ten days after the last radiation, definite tumor recession was observed, but a flat, infiltrating area to the left of the trigone extended down to the bladder neck (Fig. 12). Little, if any, change had occurred in the character of the tumor as felt on rectal examination.

About six weeks after the first x-ray treatment, on March 5, 1938, sudden death occurred from coronary occlusion. At autopsy several interesting details were disclosed. Both coronary vessels were completely occluded. Considerable congestion of the vessels supplying the small bowel was present. The intravesical portion of the malignant disease appeared flattened and shrunk to a considerable degree, but a huge, thick plaque of cancer invaded the full thickness of the bladder wall which proved to be several times more extensive than was appreciated at antemortem examination. This mass consisted of actively, growing tumor in which minor changes such as swelling of some of the cells could be attributed to radiation.

Comment.—This is a case of a highly malignant, infiltrating bladder cancer, the intravesical portion of which had been favorably affected by 6,000 r units of super-voltage radiation. Death resulting from intercurrent disease provided an opportunity for careful study of the effects of x-radiation upon the tumor. Although that portion of the growth which protruded into the bladder cavity had decreased in extent, less effect was evident upon tumor tissue which involved the deeper layers.

Case 5.—R. T. E., aged eighty-two. Huntington Memorial Hospital, August 19, 1937.

Fifteen years ago this man had a bladder tumor destroyed by transurethral fulguration. Twelve years later, I removed a papillary tumor mass from the anterior and lateral walls by a wide excision of the full thickness of the bladder. This was a highly malignant growth, carcinoma, Grade III. No known recurrence took place for nearly two years, then several pedunculated tumors appeared in several parts of the bladder, the largest being on the right anterior wall. Now he was a thin, emaciated, old man with active hematuria and pain, some anemia, red blood count 3.6, hemoglobin 65 per cent and non-protein nitrogen 33.

From August 19 to September 10, 1937, he received 7,200 r units of super-voltage radiation, 400 r units daily with no reaction. From November 4 to 10, an additional 4,800 r units brought the total x-radiation to 12,000 r units. Continued frequency and considerable pain in the region of the bladder neck was unrelieved by the treatments.

Tissue removed from the bladder neck, December 17, 1937, was actively growing cancer which invaded the prostate (Fig. 14). Considerable solid tumor was present on the right lateral wall of the bladder. His pain was eventually relieved by the intrathecal injection of 1.5 c.c. of 95 per cent alcohol.

Comment.—This is a case of recurring malignant bladder tumors of fifteen years' duration treated by transurethral fulguration,

Fig. 14. Case 5. Papillary carcinoma invading prostate. Actively growing tumor cells in a patient who had completed 12,000 r units of super-voltage radiation 1 month previously.

radical resection and super-voltage x-radiation. The growths were not controlled by any of these methods. X-ray treatment had less than the usual apparent effect on this patient's cancer, in spite of such high dosage as 12,000 r units.

Case 6.—W. B., aged forty-eight. Huntington Memorial Hospital, July 19, 1937.

An extensive and rapidly growing bladder tumor of high malig-

nancy was found in this patient, who was otherwise well. Three months previously a hopelessly large, malignant mass within the bladder was attacked by suprapubic operation at another institution. Some of the neoplasm was destroyed by electro-coagulation and a permanent tube inserted. The right kidney was already functionless and the left kidney seriously affected by pressure on the ureter. This tumor was epidermoid carcinoma, Grade III. A large, suprapubic mass of malignant disease made its appearance soon after operation but receded after sixteen treatments at one of the State institutions with the 200 kilovolt machine. Shortly after these treatments the patient was sent to the Huntington Hospital,

From July 20 to October 9, 1937, the patient received 8,400 r units of super-voltage radiation with the million volt machine. Cystoscopic examination during the course of this treatment, three weeks after he had received 6,000 r units, failed to show any definite tumor within the bladder. A month later, however, soon after completing 8,400 r units, a large amount of solid new growth was evident around the bladder outlet and the left lateral wall. At present the patient is entirely miserable and rapidly losing strength.

Comment.—This is the case of a man in the late stages of malignant bladder disease. Low voltage radiation had considerable effect on the rapidly extending malignant tissue. Super-voltage radiation of 8,400 r units had little if any added apparent effect.

Case 7.—F. S. B., aged eighty-three. Huntington Memorial Hospital, September 17, 1937.

The patient presented a very extensive papillary, infiltrating bladder tumor which surrounded the outlet and extended up both lateral walls. Attempts to control this growth or to relieve his great discomfort in any way by transurethral methods proved futile, so he was given a permanent suprapubic opening. Added to his advanced years were the complicating features of a proteus infection of the bladder, enlarged prostate and rheumatic heart disease with aortic regurgitation. Renal function was good, however. Blood pressure was 160/90, red blood count 3.6, hemoglobin 70 per cent. Tumor biopsy indicated papillary carcinoma.

Super-voltage treatment was started on September 7, 1937, with daily doses of 400 r units. In spite of his infirmities the treatments were well tolerated and by October 4 the patient had received a total of 6,000 r units. Three weeks later no appreciable change was evident in the tumor mass within the bladder (Fig. 15). Urethral pain which had been a prominent feature was not relieved by the deep therapy and eventually necessitated intrathecal injection of alcohol. In this manner pain was eliminated but rectal incontinence resulted and persisted.

Seven months have elapsed since the first super-voltage radiation.

His general condition has vastly improved, there is no evidence of tumor growth beyond the bladder, and no skin changes other than moderate suprapubic tanning.

Comment.—This is an instance of advanced bladder malignancy in a frail individual of advanced years who tolerated, nevertheless, 6,000 r units of super-voltage radiation without impairment of his health, but with no evident effect on the cancer.

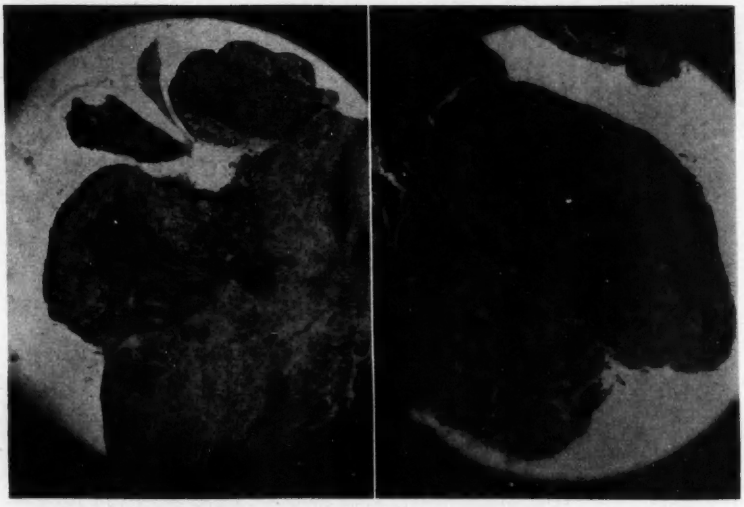


Fig. 15. *(left)* Case 7. Low power. Papillary carcinoma of bladder. Appearance of tumor after 6,000 r units of super-voltage radiation. Vacuolization of the tumor cells is evident although there was no appreciable gross change in the cancer.

Fig. 16. *(right)* Case 8. Biopsy of bladder tumor. Undifferentiated epidermoid carcinoma. Before radiation.

Case 8.—J. McE., aged seventy-three, Huntington Memorial Hospital. March 3, 1938.

This patient had a nine months' history of hematuria and pain. Much of the bladder base was covered with a flat, infiltrating tumor of considerable extent. Although the trigonal region did not appear to be involved, advancing, ulcerated, malignant disease could be seen spreading up the back wall of the bladder. No thickening of the bladder base was felt rectally. His general condition was seriously impaired by bleeding, pain and sleepless nights. Red blood count

was 4.4, hemoglobin 90 per cent. Biopsy report was epidermoid carcinoma, Grade II (Fig. 16). In the cystogram were extensive filling defects of the inferior and posterior walls.

Super-voltage radiation started March 21, 1938, with 400 r units daily. As the treatment progressed the patient became more comfortable and bleeding ceased. No serious reaction has been experienced from the x-radiation, although discoloration and thickening of the suprapubic skin is much more pronounced than in others. Still under treatment, 6,000 r units represented total radiation on April 7, 1938. Two weeks later, on April 21, 1938, the cystoscopic appearance was quite different from that of the original examination. The bladder mucous membrane was generally reddened, the area of the tumor was so edematous that neoplastic tissue could not be identified.

Comment.—This is a recent case of advanced, undifferentiated bladder cancer, under treatment with super-voltage radiation. At present 6,000 r units have been well tolerated and the tumor seems to show definite regression. Biopsy report April 21, 1938, was epidermoid carcinoma, Grade II. There has been slight radiation reaction, cells are swollen, but there are no mitotic figures.

CONCLUSIONS

A small group of malignant tumors of the bladder treated by super-voltage x-radiation with a recently devised million volt generator is reported. Although the series is entirely inadequate to evaluate fairly this form of treatment, certain tumors appear profoundly affected with considerable regression. Those portions of the tumor which project into the bladder cavity seem to be affected considerably more than those which have extended through the bladder wall. Other tumors are affected little, if any, and are considered "radio-resistant." It is not considered that super-voltage radiation, in its present state, takes the place of operation in instances of circumscribed cancer which can be adequately removed. Dosage so far employed is probably considerably less than that which is possible, but more experience is necessary to standardize dosage and determine its ultimate effect. Local and general untoward reaction is less than with lower voltages and tumor regression more evident.

The kind help and coöperation of Dr. Richard Dresser in the preparation of this report is greatly appreciated.

REFERENCES

1. COLWELL, H. A.: The method of action of radium and x-rays on living tissues. London: Oxford University Press, 1935.
2. FOGG, L. C., and WARREN, S.: A comparison of the cytoplasmic changes induced in the Walker rat carcinoma 256 by different types and dosages of radiation. Am. Jour. Cancer, 31:567-584, (December) 1937.
3. TRUMP, J. G., and VAN DE GRAAFF, R. J.: Design of a million volt x-ray generator for cancer treatment and research. Jour. Applied Physics, 8:602-606, (September) 1937.

DISCUSSION

Dr. J. A. C. Colston (Baltimore, Md.): I should like to ask Dr. Colby whether he has noticed the sudden occurrence of metastasis a short time after deep x-ray therapy. The reason for this question is that we have noted in two recent cases the rapid appearance of metastasis within a few months after the completion of a course of deep x-ray therapy. These observations, of course, may have been entirely coincidental. The first patient had a nodular infiltrating tumor over the right side of the bladder wall and the prostate was definitely infiltrated on rectal examination. On completion of a course of deep x-ray therapy, to our great surprise, the tumor had completely disappeared on cystoscopic examination and the infiltration was no longer palpable per rectum. About six weeks later, however, symptoms of a brain metastasis appeared, from which the patient died. Autopsy showed the bladder mucosa to be smooth and the tumor had apparently completely disappeared, but sections through the bladder wall showed a few strands of definitely viable cancer cells between the muscle bundles.

The second patient had an infiltrating nodular tumor involving the dome of the bladder. This tumor was not very extensive and it probably could have been resected, but the patient refused operation and asked to be given deep x-ray therapy. After the completion of a course, we were again surprised that the tumor, on cystoscopic examination, had completely disappeared. Within two months, this patient developed symptoms of clinical carcinomatosis, from which he died. No autopsy could be obtained. These cases were a great disappointment as, of course, we were greatly pleased with the prompt disappearance of the tumors locally, and we could not refrain from the inference that deep x-ray therapy may have had some bearing upon the rapid and unexpected development of metastases.

Dr. Leon Herman (Philadelphia, Pa.): Unlike Dr. Dean, I am incapable of discussing the physics of irradiation intelligently. However, when the New York Urological Society had a meeting with us in Philadelphia recently we demonstrated a method of

treating cancer of the bladder by direct irradiation with the apparatus illustrated by Dr. Dean today. Our method differs from that of Dr. Dean in that we marsupialize the bladder and give repeated doses of irradiation as circumstances dictate. It has been my impression that cancer of the bladder, with few exceptions, is rather radio-responsive and that failure to cure cancer by means of irradiation is due principally to the fact that the potency of the rays is largely lost in transit through the superficial tissues. Marsupializing the bladder and applying the rays directly to the tumor as often as seems desirable would appear to be an ideal procedure. We have not had enough experience with the method to justify any opinion whatsoever except that from the mechanical standpoint the procedure seems to be a very practical one.

In preparing the bladder we make a midline incision, open the bladder widely, and mobilize it sufficiently to permit union of the edges of the bladder to the skin margins. The margins of the bladder are anchored above and below, thus isolating the space of Retzius and minimizing the occurrence of hernia above. In repairing the defect the midline incision should be closed after mobilizing, closing, and restoring the bladder to its normal position, and counter drainage used through the rectus muscle on either side. It is my belief that if x-ray irradiation is capable of curing neoplasm of the bladder by direct application, this method offers a practical solution of the problem.

DR. ARCHIE L. DEAN: I have recently learned of several urological clinics in which attempts have been made to control bladder tumors by direct irradiation. In each case the bladder was marsupialized and treated with divided doses. I am attempting something quite different in trying to devise a method of controlling the bladder tumor by a single treatment. Whether or not it can be successful I do not know. However, I have every confidence that the physicists, who, after all, must first design more efficient apparatus for us, are now developing x-ray tubes and units which are far better than anything we now have. After a time we may know what can and can not be accomplished by this means.

DR. FLETCHER H. COLBY (Boston, Mass.): In answer to Dr. Colston: Some of these patients, of course, whose tumors are

radio-resistant, are doing very badly, and obviously have not been benefited by treatment. While there is no obvious evidence of metastatic disease in them, I don't see any reason why they shouldn't have just as much as others.

This form of very high voltage radiation has certainly been given incomplete trial. We are enthusiastic about it up to a certain point, but are trying to evaluate the method fairly. It appears as if these elderly people with advanced cancer will tolerate higher doses of this form of radiation with its very short wave length considerably better than lower voltages. The ionization chamber has appeared to show that a 20 per cent larger depth dose is delivered by this machine than with the 400 kilowatt volt machine.

TRANSPLANTATION OF ENDOCRINE TISSUE

PRELIMINARY REPORT ON EXPERIMENTAL WORK

WILLIAM E. LOWER, M.D., and (by invitation) EUGENE CUTULY, Ph.D.

Cleveland, Ohio

When an endocrine gland is destroyed by disease or operation, treatment in most cases comprises substitutional therapy administered orally or by injection and this generally must be continued for the remainder of the patient's life. In these cases, substitution of a functional gland is the desideratum for which everyone hopes.

The successful transplantation of tissues, however, is not a simple matter and depends upon a large number of factors, some of which concern the graft itself and others the host. To any graft, for example, a host may set up a natural defense reaction to injury or the introduction of a foreign body. Other factors of great importance are related to proper vascularization of a graft and the age, time, and relation of the transplant to the host. In considering the relation of the transplant to the host, there arise such questions as the autoplastic, homoplastic, or heteroplastic character of the tissues and the genetic compatibility between tissue and host. Loeb and Wright[2] have stressed the importance of considering the genetic constitution of both donor and recipient.

Studies on sub-human animal grafting have almost invariably shown that heterotransplantation, that is, transplantation between different species, is unsuccessful. Such studies lead one to regard with caution the announcement that heteroglandular grafting in human beings has brought favorable returns (Voronoff).[5]

Homoplastic grafting in human subjects is a more logical procedure than heterografting. The preliminary studies of Stone, Owing, and Gey and more recently those of Gey,[1] who used the tissue culture technic, offer considerable promise. Gey has reported that more than one-third of a series of sixteen patients with marked parathyroid tetany are well from two to six years after homologous grafting with tissue cultures.

In well documented works (Werner),[6] the scanty literature dealing with successful transplantations in human subjects attests to the relatively little knowledge there is about this subject. On

the other hand, there is a vast literature on the subject of transplantations in sub-human animal forms. Much information has been derived from studies on transplantations of glands in rats. The studies to be reported here have been made on the rat, the technical work and the follow-up studies having been done by Eugene and Elizabeth Cutuly.

In our work, the first factor to be considered was determination of a suitable site for grafting of the glands. The tip of the ear seemed satisfactory because it readily afforded a good supply of blood and because the growth of a transplant could be watched from day to day.

Grafting to the ear is a comparatively simple procedure. About midway between the tip and the base of the dorsal side of the ear a short incision is made through the skin. The blades of scissors are inserted through this incision into the subcutaneous tissues and spread apart gently a number of times until a subcutaneous pocket has been formed. Tissue to be grafted is inserted through the opening of this pocket and gently pressed toward the tip of the ear. Sutures are not needed to keep the grafts in place or to close the slit in the skin. Usually there is a little hemorrhage.

By this method, we have made more than 100 grafts into the ears of rats. All experiments in which adult tissues were used as transplantation material gave negative results. We have, however, had remarkable success with grafts from newly-born donor rats. The following tissues have been grafted: testis, prostate, seminal vesicle, pituitary, ovary, adrenal, thyroparathyroid, and pancreas.

Testis grafts have taken well both in castrated hosts (thirty out of forty cases) and in normal hosts (twenty out of thirty cases).

Accessory sexual organs, such as seminal vesicles, have grown in the presence of testicular male hormone (three cases out of three) but have uniformly failed to grow in castrated animals (ten cases).

Adrenal grafts have also uniformly failed to take in normal animals, but one adrenalectomized animal, bearing a homoplastic adrenal graft in the ear, is still alive more than one month after adrenalectomy.

Two thyroparathyroid grafts have taken in normal animals.

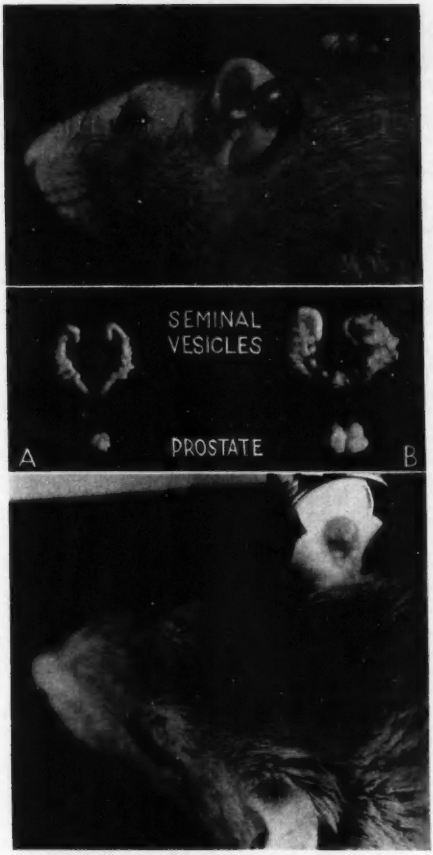


Fig. 1 *(top),* Host: Castrated male rat. Ear in foreground shows testis from rat one day old, transplanted four months previously. Ear in background shows prominence made by seminal vesicle grafted simultaneously with testis.

Fig. 2 *(center), A,* From a castrated male rat. *B,* From a castrated male rat with a functional testis graft in the ear. Tissue from a rat one day old had been grafted two months before photograph was taken.

Fig. 3 *(bottom),* Host: Castrated male rat. Seminal vesicle graft in ear transilluminated to show secretion (light areas). Flashlight bulb in background. This graft was stimulated by hormone from a testicular graft in the other ear.

In six cases of ovarian grafts, distinct nodules have formed at the site of transplantation, but where the hosts are spayed females these nodules have apparently not been functional, as the spayed animals have not yet shown estrous vaginal smears.

Our results with transplants of the pituitary and pancreas are at present indefinite.

At the present time, we are interested primarily in reporting some of the results obtained with testis grafts.

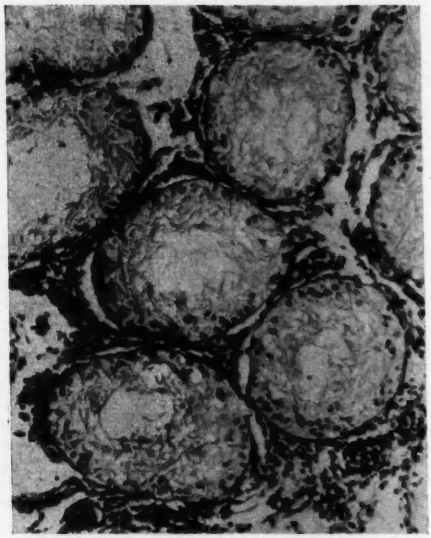


Fig. 4. Testis from rat one day old taken from ear of a castrated host four months after transplantation.

Testes which have been grafted to the ears of castrated rats (Fig. 1) develop and produce male hormone, as judged by the return of the host's atrophied accessory organs toward a normal condition (Fig. 2), or by stimulation of grafted accessory sexual tissue (Fig. 3). Since male hormone is elaborated by the interstitial component of the testes, it would be expected that the graft seen in Figure 1 would possess normal interstitial cells. This is confirmed histologically in Figure 4. This experiment establishes

the fact that a testis grafted in a subcutaneous pocket in the ear will produce sufficient male hormone to stimulate the seminal vesicles and prostate.

It is known that testes transplanted to other subcutaneous sites, as well as those transplanted to the scrotum, also may become functional. Scrotal grafts of testes differ from subcutaneous grafts in that the former may produce mature spermatozoa, as well as functional interstitial cells. Testes transplanted subcutaneously or interaperitoneally have never been known to develop spermatozoa (Moore).[3] This brings up one of the fundamental concepts concerning testicular physiology.

In most mammals a scrotum is absolutely essential to spermatogenesis. Perhaps it would be more accurate to say that it is the thermoregulation effected by the scrotum which is essential to spermatogenesis. There is some evidence, in fact, which indicates that spermatozoa may develop in testicular tissue growing outside the scrotum—in the anterior chamber of the eye (Turner).[4] However, it was shown in these studies that the temperature of the anterior chamber of the eye is quite similar to that which obtains in the scrotum. It is hoped that the tip of the ear, too, may in some way be made to provide testis grafts with an environment favorable to spermatogenesis. While this has not been possible thus far, it may be that grafts transplanted for periods longer than four to six months will show some activity of the germ cells. Studies to determine this question are in progress.*

SUMMARY

The material presented here is preliminary. Thus far it has been our purpose to develop a technic which will yield consistently good returns. When this has been accomplished, data will have accumulated which can be used as a standard for future studies. It is our plan to study in greater detail factors which are concerned in the successful or unsuccessful incorporation of grafted endocrine tissue in related and unrelated hosts. It is hoped that the results of our investigations will help in the understanding of principles which may apply to the problem of transplantation in human beings.

*There is some recent evidence which indicates that some germ cell development can occur in testis tissue grafted in the ear. Microscopic examination of a testis from a newborn rat grafted to the ear and removed several months later revealed the presence of spermatogonia and primary spermatocytes in the tubules.

REFERENCES

1. GEY, G. O.: Some problems in the maintenance of tissue cultures of endocrine organs to be used for transplantation purposes in cases of specific endocrine deficiency. Anat. Rec., 70:30 (Supplement), (March) 1938.
2. LOEB, L., and WRIGHT, S.: Transplantation and individuality differentials in inbred families of guinea pigs. Am. Jour. Path., 3:251-283, (May) 1927.
3. MOORE, C. R.: Sex and Internal Secretions, Chapter VII. Baltimore: Williams & Wilkins, 1932.
4. TURNER, C. D.: Intra-ocular homotransplantation of prepuberal testes in the rat. Anat. Rec., 70:80 (Supplement), (March) 1938.
5. VORONOFF, S.: Results followed up for twenty years after grafting of the thyroid in cases of myxedematous cretinism. Bull. Soc. de Path., Comparee (Paris), No. 492, (October) 1937.
6. WERNER, A. A.: Endocrinology. Clinical Application and Treatment, Philadelphia: Lea and Febiger, 1937.

NON-SURGICAL CLOSURE OF VESICOVAGINAL FISTULA

VINCENT J. O'CONOR, M.D.
Chicago, Illinois

The treatment of vesicovaginal fistula is quite generally considered a problem of gynecologic or general surgery. However, Kelly, a pioneer gynecologist and cystoscopist, has always stressed the advisability of careful cystoscopic investigation and the routine catheterization of the ureter for protection during the operative repair.

Many operations for the closure of vesicovaginal fistulæ are conducted without careful urologic study, and certain types of fistulæ which might be closed by more simple urologic treatment are frequently subjected to extensive surgical procedures. Multiple operations often reduce the size of the fistula without affecting the necessary closure that restores normal bladder function. It is generally recognized that the frequency of healing decreases after each operation for repair of these fistulæ.

The purpose of this report is to emphasize the possibility of success in closing less extensive defects by cystoscopic and vaginal coagulation of the tract and proper prolonged postural drainage of the bladder by means of an indwelling urethral catheter. This procedure has received little or no consideration in the voluminous literature on the subject of vesicovaginal fistula. One finds no mention of it in standard texts on gynecology. Zabrowski,[3] in a recent article, states that the most important conservative method of treating the fistula is permanent catheterization. Of forty-five cases collected from the literature in which this procedure alone was employed, healing resulted in ten. Ottow[1] has advocated electrocoagulation for small vesicovaginal fistulæ and recommends that an indwelling catheter be left in the bladder for ten days. Quinby[1] has reported the final healing of vesicovaginal fistula after cystoscopic electrocoagulation when closure of the defect by surgical repair had not been complete.

The following personal experiences are given in the hope of stimulating more interest in this subject, both among urologists and surgeons in general.

CASE REPORTS

Case 1.—In August, 1922, I was asked to see a woman, aged twenty-four, who had been suffering from a vesicovaginal fistula for two years. The fistula resulted from incision of the bladder during a vaginal sterilization operation, the latter having been done some weeks after an induced abortion necessitated by an extreme thyrotoxicosis. Prior to my seeing her, two unsuccessful attempts had been made at vaginal closure by her gynecologist. On each occasion the patient had a very stormy time and barely came through the immediate postoperative convalescence. Although the incontinence of urine was complete, cystoscopy showed the fistulous opening to be only about 0.5 cm. in diameter and located about 1.5 cm. above and just medial to the left ureteral orifice. I suggested coagulation of the fistula both from the bladder and vaginal sides, with the idea that the fistula might close spontaneously. This was done, using a light current with just enough desiccation to thoroughly destroy the epithelial tract. The patient returned home and showed no improvement for one month, after which time she began to void from three to four ounces at a time but continued to drain partially through the vagina.

Encouraged by this partial closure, I felt that if the area of the fistula could be kept relatively dry during the sloughing and healing stage, complete closure might be effected. We prepared a bed in the hospital by cutting a hole in the mattress so that the patient could lie on her abdomen and have an indwelling catheter drain directly into a bottle beneath the bed. The fistula was again desiccated both fore and aft and an indwelling catheter inserted. The patient maintained a position on her abdomen for three weeks without vaginal leakage. Removal of the catheter showed a complete closure of the fistula and a bladder function which quickly returned to normal. This patient has remained well and in July, 1928, had a thyroidectomy and is now reported in splendid health.

Case 2.—I did not see a similar case in which this treatment seemed suitable until September, 1928, when I was asked to see a woman, aged forty-eight, who had had a vaginal hysterectomy in February, 1926 with resultant vesicovaginal fistula, apparently from the sloughing around a deeply placed chromic catgut suture. One attempt at vaginal closure had been unsuccessful in the hands of a skilled gynecologist. As is well known, vaginal closure in previously vaginally hysterectomized patients is frequently very difficult. On cystoscopy this patient had a fistulous opening just to the right of the midline, somewhat above the bas fonde and 0.5 cm. superior to the right ureteral orifice. The fistulous tract admitted a No. 12 F. bougie easily. Coagulation of the area and the tract (inserting the electrode directly into the fistula) with a fine desiccating current; insertion of a No. 24 F. mushroom indwelling urethral catheter and maintaining the patient in a completely upright sitting posture on a specially prepared

backrest for four weeks resulted in complete and permanent closure of the fistula.

Case 3.—In February, 1936, we were consulted by a woman, aged fifty-eight years, who had had a supravaginal hysterectomy in October, 1934. In this instance a deeply placed chromic suture had apparently sloughed through the bladder wall, causing a vesicovagnial fistula.

In March, 1935, an unsuccessful attempt to close this fistula by vaginal surgery was accompanied by a severe ileus and a prolonged hospital convalescence of three months. The surgeon in this case was a man of undoubted ability and he had later advised this patient that he could close the fistula by a combined suprapubic and vaginal operation. Because of the difficult convalescence she had had, this patient was loath to enter upon another surgical experience. On cystoscopy the fistulous opening admitted a No. 14 F. bougie snugly. The opening was located 0.5 cm. above and just medial to the left ureteral orifice. Embedded in the tissue superior to the opening, a darkened area suggested the presence of a piece of chromic catgut. Desiccation both vesically and vaginally was performed in the office and a No. 22 F. mushroom catheter fixed in the urethra. A backrest was purchased and placed on her bed at home; the catheter drained into a bottle at the bedside.

The patient stayed in the upright sitting posture for four weeks. She was allowed to stand at the bedside several times each day, the catheter being disconnected by the nurse on these occasions. On removal of the catheter cystoscopy showed complete closure of the fistula. This patient has normal bladder function and has been able to resume all her activities, including golf and horseback riding.

Case 4.—In July, 1936, a woman, aged forty-five years, presented herself with a condition almost identical with the preceding patient. In 1933, a diagnosis of early carcinoma of the cervix uteri was followed by vaginal application of radium. Six months later a total supravaginal hysterectomy was done by one of our most skillful gynecologists and to his dismay, the patient developed a vesicovaginal fistula. (He states that this is the only instance in 2,800 hysterectomies). In July, 1935, this gynecologist, assisted by one of our most competent urologists, was unsuccessful in closing the fistula by a combined suprapubic, intravesical and vaginal repair.

Sections of the uterus removed in 1935 had failed to show evidence of carcinoma in cervix or body of the uterus. In July, 1936, incontinence had been complete since the previous operation. The fistula was situated just above the inter-ureteric ridge 1.0 cm. medial to the right ureteral orifice. A No. 14 F. bougie seemed to fill about two-thirds of the lumen of the fistula. There was no evidence of infiltration suggestive of malignancy in this region. The fistulous tract was completely coagulated through the cystoscope, the vaginal exposure

being unsatisfactory. A No. 24 F. mushroom catheter was inserted in the urethra and the tubing attached to a mild suction bottle at the bedside.

The patient maintained an upright sitting posture, with slight pillow elevation of the hips, for twenty-eight days. On removal of the catheter the patient voided from 150 c.c. to 300 c.c. of urine at a time but there was slight dribbling when she was up and about. There was no incontinence when lying in bed. The dribbling ceased in ten days and was apparently urethral in origin, due to the prolonged presence of so large an indwelling catheter. Cystoscopy six weeks later showed complete healing of the bladder and normal function has continued.

Successful closure in these four instances was accomplished by (1) destruction of the epithelial tract and subsequent freshening of the edges; (2) indwelling catheter drainage with postural attempt to keep fistulous area as dry as possible; (3) continuous acidulation of the urine to prevent lime encrustation of the coagulated tissue. In the last two patients described, this was accomplished by an acid-ash diet and doses of ammonium nitrate large enough to maintain a Ph of 5.5 or lower.

Two instances of the relation of syphilis to the healing of vesicovaginal fistula are worthy of record.

Case 5.—In January, 1928, a twenty-four year old society matron stated that in August, 1926, she had been delivered of her first child by forceps and had developed a vesicovaginal fistula. She had been in excellent obstetric hands and the incident had caused considerable embarrassment. In June, 1927, she was operated upon by one of America's best known gynecologists. The fistula was closed for three weeks but re-opened with complete incontinence. Examination in January, 1928, showed a very small fistulous opening in the bas fonde midway between the ureteral orifices. Traction on the cervix brought the vaginal opening of the fistula into excellent view. I could not understand why so competent a surgeon had failed to effect a closure and assured the patient that I could make a surely perfect repair from the vaginal side.

The operation was so easy and so satisfactory that I made no attempt at keeping the area dry by posture, although an indwelling catheter was retained for three weeks. The patient voided normally without leakage for forty-eight hours, after which time partial urinary leakage recurred from the vaginal tract. I was puzzled and discouraged until my fingers fell upon an enlarged epitrochlear node which I had overlooked but the presence of which the intern had recorded on her chart. The blood Wassermann (previously omitted from the routine) was returned as four plus. Re-insertion of an indwelling catheter and intravenous arsphenamine resulted in a complete

closure of the tract in fourteen days. Subsequent antiluetic treatment and observation until July, 1931, showed no recurrence and serologic cure.

Case 6.—In March, 1928, with the previous experience freshly in mind, we were consulted by a Mexican girl, nineteen years of age. She was completely incontinent from a small vesicovaginal fistula following her second delivery four months previously. The blood Wassermann was four plus. The fistula admitted a No. 8 F. bougie and was 0.5 cm. above and medial to the right ureteral orifice. Intravenous arsphenamine, without indwelling catheter or other local measures, resulted in complete closure of the fistula after fourteen days. The patient was observed for another two weeks, during which time her bladder functioned normally. She then disappeared and has not been seen since.

CONCLUSIONS

Small vesicovaginal fistulæ with healthy surrounding tissue will heal after electrocoagulation, if postural drainage can be maintained with indwelling catheter for a sufficient period of time. The possibility of this method should receive more consideration, especially in patients upon whom an unsuccessful surgical repair has resulted in a small, lateral opening. The method obviously has no place in the treatment of fistulæ of the bladder floor or where extensive tissue defect exists.

BIBLIOGRAPHY

1. Ottow, B.: Zentralbl. f. Gynäk., 54:1093, (May 3) 1930.
2. Quinby, William C.: New England Jour. Med., 214:415-417, (Feb. 27) 1935.
3. Zabrowski, Francis L.: Cyclopedia of Medicine. Philadelphia: F. A. Davis, Vol. V, p. 710.

DISCUSSION

DR. WILLIAM E. LOWER: If I may be permitted a few minutes, I should like to read Dr. Cutuly's written discussion, inasmuch as he is not here.

The results presented in this report are of particular interest from an experimental point of view for two reasons.

1. The technic described enables one to correlate very intimately the physiology and morphology of the testes.

2. The technic described may prove to be a most valuable means for studying factors intrinsically associated with spermatogenesis.

(1) A graft in the ear can be observed from day to day. This is especially important in instances where a castrated rat is carrying a graft of testis in one ear and a graft of seminal vesicle grafted in the other ear. Since seminal vesicle and prostate do not grow in the absence of testicular hormone, growth of seminal vesicle grafted in the ear of a castrated rat which also bears a testis graft must be attributed to the hormone produced by the testis graft. It is thus possible to determine almost exactly when a graft begins to function.

In this connection it might also be pointed out that an externally grafted seminal vesicle and testis can be of great service in studies to determine either injurious or stimulating effects of substances on the testis. For instance, let us consider the case where a castrated rat has seminal vesicle in one ear and testis in the other. Provided both the transplants have taken, the seminal vesicle will grow under the influence of the male hormone produced by the testis graft. Growth of the seminal vesicle, however, would cease very quickly if the host is injected with substances injurious to the testicle. The contrary would also be true. If the testis graft is stimulated by substances injected into the host, then the seminal vesicle would show increased stimulation. Observations of this kind would be particularly useful in making rapid determinations. Another advantage to this type of study would be that animals would not necessarily have to be sacrificed, as all necessary observations could be made grossly. Of further interest in this regard would be the possible use of such material for the study of re-

covery effects. In other words, if one should be interested in determining whether injurious agents permanently destroyed testis tissue or merely temporarily suppressed its activity, the grafting method should be very practical. Not only would it not be necessary to kill animals to obtain internal organs, but also it would be possible, on grafted tissues, to make repeated determinations of growth and regression and the time necessary for such changes to occur.

(2) With respect to the question of spermatogenesis, it is necessary to recall that considerable doubt exists about the factors involved. Until recently, it was believed that spermatogenesis was under the control of an anterior pituitary hormone known as the gametokinetic or gametogenic hormone. Studies made in our own laboratory, however, have proved conclusively that spermatogenesis can occur in the total absence of the pituitary gland. In brief, these studies showed that when male hormone was administered to hypophysectomized rats, the tubules of these animals continued to produce mature germ cells—despite the fact that the animals were without any pituitary secretion whatsoever. Another observation made in this connection was that the testes of such hypophysectomized animals injected with male hormone always resided in turgid, flushed scrota. Since it is a well established fact that most mammals require a scrotum for spermatogenesis to occur, it seemed to us that there was a possibility that spermatogenesis in hypophysectomized rats treated with testicular hormone progressed because the male hormone maintained the scrotum—which atrophies in untreated hypophysectomized rats—and thus provided the proper environment for germ cell development to occur.

There are some who contend that male hormone has a direct stimulating effect on the germinal cells. Critical proof of this view, as well as critical proof of the view involving the scrotum as proposed by us, is still lacking. As a matter of fact, controversy over this point has temporarily reached an impasse, since until recently no one had been able to demonstrate spermatogenesis in any testes except those inhabiting a scrotum. Because of the inseparability of the scrotum and spermatogenesis, it is obvious that it could never be said conclusively whether spermatogenesis was stimulated directly or whether it was induced to occur because the

germ cells were provided with a properly thermoregulated environment. Recent studies have indicated that spermatogenesis may occur in testis tissue grafted to the anterior chamber of the eye. These studies have also shown that the temperature of the anterior chamber of the eye closely approximates that in the scrotum—which is several degrees lower than the temperature anywhere else in the body.

It is hoped that spermatogenesis can be induced to occur in testes grafted to the ear. This location would be ideal, since it would allow for considerable growth of the graft and at the same time be suitable for gross observations. If spermatogenesis can be induced in testis grafts in the ear, it seems fairly certain that it will be possible to ascertain whether male hormone has a direct or indirect effect on germ cell differentiation. For example, let us assume that a normal male rat (possessing normal testes of its own) also is carrying a functional graft of testis in the ear. Let us also assume that this graft is carrying on spermatogenesis. If such an animal were hypophysectomized and injected with male hormone, one thing is already certain: the normal testes would remain in the scrotum and continue producing mature spermatozoa. But what would happen to the graft under these conditions? Would spermatogenesis continue here as well, or would it cease? If spermatogenesis continued it would be fairly strong presumptive evidence that male hormone affects germ cells directly. If spermatogenesis ceased in the ear graft (and not in the scrotal testes) then it would be fairly strong presumptive evidence that the scrotum—or, more properly, the beneficial effects exerted by the scrotum—and spermatogenesis are very intimately associated.

THIRD DAY, MAY 4, 1938

RESECTION OF PROLAPSED MUCOSA AT THE VESICAL NECK FOR RETENTION OF URINE IN THE FEMALE*

JOHN H. NEFF, M.D.

From the Department of Urology, University of Virginia, University, Virginia.

This report is based primarily upon the observations made in two adult women and the treatment employed for their relief. The essential features from their records will serve as the best introduction to a brief discussion of a seemingly rare cause of retention of urine.

Case 1.—A widow, aged seventy-nine, was admitted to the hospital January 16, 1936, because of inability to void. Two years previously she had developed the symptoms of a cystitis. Frequency, urgency and dysuria had gradually increased over the next eighteen months in spite of irrigations, cystoscopic and other instrumental treatments elsewhere. Complete retention then occurred. For the six months preceding admission she had catheterized herself four or five times daily.

The patient was well preserved, mentally alert and physically active. She had managed her own farm for some years. She had never been pregnant.

Careful study furnished no pertinent information beyond the findings in the urinary tract. The centrifuged sediment of the catheterized urine showed many bacilli and fairly numerous pus cells. The urethra admitted sounds through 34 F. without the least difficulty. Vesical capacity was 350 c.c. Tone of the bladder seemed normal.

Cystoscopic Observations.—Trabeculation was as marked as in an old prostatic patient. The mucous membrane presented the changes of a low-grade inflammation. The net result of visualization of the vesical outlet through the indirect cystoscope, the McCarthy panendoscope and, finally, an open endoscope, was the demonstration of a ring of loose mucosa at the internal urethral orifice which jammed the urethra at each effort to void. This was best shown with the patient in the knee-chest posture while the bladder was full. As the urethroscope was withdrawn from the bladder into the urethra, the patient straining vigorously all the while, the forceful flow of fluid would suddenly stop. After clearing the endoscope, the plugging ring of prolapsed tissue was obvious. (Fig. 1). There was no evidence of sclerosis to inspection, instrumental manipulation or vaginal palpation upon an instrument in the urethra.

The patient was catheterized regularly until resection on January 21, 1935. Some six bites were then taken from the redundant tissue with the McCarthy resectoscope. The cuts were limited to the posterior half of the orifice. The retention catheter was taken out after forty-eight hours. Patient voided freely during the next five days but had a residual urine varying from 30 to 110 c.c. On January 28 the remaining loose tissue anteriorly was excised along with several more bites pos-

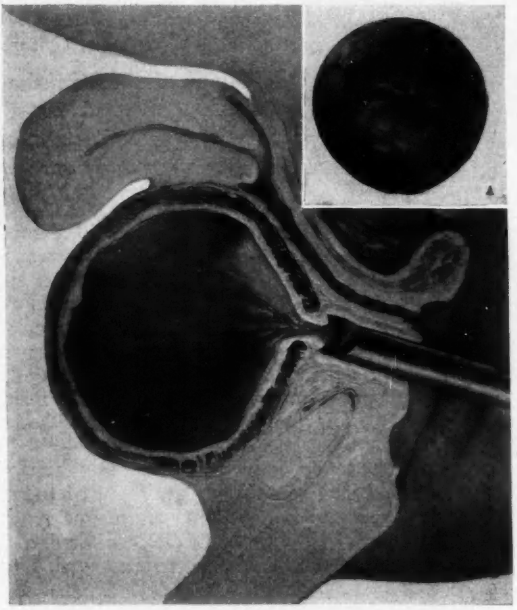


Fig. 1. Illustration of the impression obtained of the anatomic change in Case 1. The insert shows the endoscopic appearance of the prolapsus. The picture in Case 2 was essentially the same save that the apex of the prolapsed ring extended slightly further down the urethra.

teriorly. Two days later her capacity was 250 c.c. and the residual 15 c.c.

Pathological Report.—Mucosa was of transitional type and was considerably altered by the extensive down-growth of very thick projections into the submucosa. Some of these cords showed cystic centers. Others had distorted lumina lined by a layer of cells simulating high

columnar epithelium. The submucosa was thick, composed mainly of collagen with an abundant cellular infiltration. Numerous veins and arteries were dilated. A considerable amount of smooth muscle, similar to that of the bladder, showed no change of note (Fig. 2,*A*).

The patient was closely followed until her death from pneumonia in January, 1936. During these twelve months she had perfect control, voided about six times in twenty-four hours, was free of vesical discomfort. Her residual urine stabilized at 20 to 25 c.c. At no time was there any tendency to the formation of a stricture at the site of the resection.

Case 2.—A married woman, aged thirty, was referred to the Surgical Out-Patient-Department, December 20, 1936, with a diagnosis of abdominal tumor. Catheterization obtained 1900 c.c. of urine and prompt disappearance of the tumor. She was admitted to the hospital January 3, 1937. The residual urine then measured 1750 c.c.

Her statements were always too vague to furnish a satisfying history. Seemingly there had been increasing frequency, both by day and by night, for an uncertain number of years. The husband reported that she had had a marked nocturnal incontinence on numerous occasions for at least two years before admission. In early December, 1936, low abdominal pain and lumbosacral backache became almost constant. These complaints were not correlated with dysfunction of the bladder, though she was then voiding small amounts at close intervals and had an evident mass above the symphysis.

Nothing of significance for this report was revealed by general physical, neurologic and gynecologic examinations. Wassermann tests were negative both on the blood and spinal fluid. Blood urea reading was 42 mg., two hour phthalein output was 50 per cent. She had two living children and had had four miscarriages. The catheterized urine showed a few pus cells and gram-positive cocci.

Under regular catheterization and the later use of the continuous irrigation apparatus of Hinman, the bladder rather rapidly contracted to a maximal capacity of 250 c.c. On repeated trials she could never void more than a very small amount. The urethra readily admitted sounds through 33 F. The first cystoscopy, January 5, revealed a trabeculated bladder, a low-grade cystitis, bilateral pyelitis with a stasis of 30 c.c. on each side. Nothing was demonstrated at this examination to explain the retention of urine. A cystogram on January 6 gave no evidence of ureteral regurgitation. The cystometric tracing, January 7, was normal.

Cystoscopic studies were repeated on January 29. It was then recognized that she had a ring of redundant mucosa in the urethra shortly outside of the bladder while the internal urethral orifice itself appeared definitely relaxed. The mechanism of the obstruction was best appreciated with the patient in the knee-chest posture while an open endoscope was in position. Upon withdrawal of the tube from the filled

Fig. 2. *A*, Characteristic field from tissue of Case 1. Epithelial down-growth simulating gland formation is well shown. *B*, Similar field from Case 2. Neither photomicrograph includes the more deeply placed bundles of smooth muscle.

bladder, the strong flow would promptly cease, in spite of the patient's expulsive efforts, as the bulging, redundant mucous membrane suddenly plugged the canal.

Resection was done on February 3. The abnormal mobility of the encircling redundant tissue was clearly evident as it was manipulated with the loop of the resectoscope. The change was quite the opposite of a rigid fibrosis. The entire ring of tissue was removed and the aggregate bites weighed 2.5 grams.

Pathologic Report.—Transitional mucosa was in many places perfectly normal; in others there were broad down-growths, some of which appeared as branching cords of great complexity, and one showed cystic degeneration; in still others it is heavily keratinized. The submucosa was edematous, thicker than normal and showed subacute inflammatory changes. Bundles of smooth muscle, characteristic of those seen in the bladder wall, were separated by a rather conspicuous network of connective tissue in which there was a quite extensive cellular infiltration (Fig. 2,*B*).

When the catheter was removed after four days, vesical capacity was only 75 c.c. The next day the bladder was distended under pressure to 200 c.c. and the patient promptly returned this amount with a large, forceful and continuous stream. However, she was then having marked nocturnal incontinence, slight incontinence during the day. Control gradually returned. Two months later she usually was going through the night without voiding and without leakage. If she allowed her bladder to get quite full during the day, she might lose a few drops before getting to the toilet. The bladder easily held 525 c.c. and was emptied of this amount with a normal stream. One year after the resection the bladder was functioning normally, there was no residual urine, no evidence of stricture and the urine was pus-free.

In the urological literature of the last two decades, one finds scattered articles, beginning with that of Caulk in 1921, dealing with sclerosis, contracture, dysectasia of the vesical neck in women. The first twelve titles in the appended bibliography have to do with such obstructive changes in this sex. The clinical histories of the thirty-two patients discussed in these dozen reports are, in a general way, quite similar to the two detailed above. All recount difficulty in urination, the majority a significant residual urine and many complete retention. Relief for two of these patients was obtained after protracted dilatation, three were cured by the suprapubic excision of a wedge anteriorly or posteriorly from the vesical outlet. The remainder had transurethral operations, either resection with the punch or resectoscope or, in one instance, incision with the electric knife. The results of the

transurethral procedures were uniformly good. Fibrosis and inflammation were the invariable pathological findings whenever the removed specimen had been studied histologically.

It is clear from the discussions accompanying some of these papers, as well as from passing references in other papers devoted to vesical neck obstruction in the male, that there are many similar cases hidden in the files of urologists. A search, however, for descriptions of obstructive lesions exactly or even approximately like those present in my two patients has been unsuccessful. Such seeming uniqueness must no doubt be more apparent than real.

The most striking anatomical feature in my patients was a loose, redundant ring of mucosa surrounding the internal urethral orifice and which, under suitable conditions of observation, could be seen to jam the first part of the canal. In this state, the appearance of the plugging tissue, as viewed through the endoscope, was quite analogous to what one might see could the beginning of an intestinal intussusception be instrumentally inspected. The apex of the prolapsed tissue extended at least 5 mm. farther into the urethra in the second patient than in the first. For the former the internal urethral orifice was abnormally relaxed but relaxation was not evident in the latter. It was thought that the gradual return of control in the second patient corresponded to the rate of resumption of normal tone at the outlet.

So-called and quite comparable prolapse of the mucosa is well recognized for other hollow viscera. For example, we have prolapse of the gastric mucosa into the duodenum, prolapse of the ureteral mucosa into the bladder and the commonly observed prolapse of the urethral and rectal mucosa at their respective orifices. Tissue alterations and physical factors which are accepted to explain these pathological protrusions could apply, with equal logic, to the vesical outlet. As a matter of fact, when one reflects on the trying vicissitudes to which fate subjects many bladders, it seems surprising that prolapse of the vesical mucosa into the urethra is not of frequent rather than rare occurrence.

Grossly the resected pieces of tissue from both patients were small, soft and the mucosa congested and velvety. Microscopically the epithelium as a rule was much thickened and exhibited extensive and complicated down-growths. The changes of cystitis

cystica were evident in slight degree in both specimens. Certain gland-like structures in the submucosa were interpreted as extensions from the epithelium. The submucosa was unusually thick and both it and the subjacent bundles of smooth muscle showed much cellular infiltration. In no sections was there sclerosing fibrosis.

The McCarthy resectoscope proved an ideal instrument for the operative treatment of these two women. The movable loop was a very real aid in gauging the amount and abnormal mobility of redundant tissue. Perfect vision could be maintained as each cut was made and the extent of the excision had to be determined solely by vision. There was no palpable difference in the thickness of tissue between the instrument and a finger in the vagina before and after the resections were done.

The resection of the first patient was undertaken with no little timidity and had to be repeated to obtain a satisfactory functional result. In both operations it was necessary that bites be taken from the whole circumference of the urethra. Meticulous care is obviously in order for such work but one familiar with the female urethra and accustomed to using the McCarthy resectoscope should incur no serious risk of causing a vaginal fistula or of injuring the sphincters. The latter, while nearby, are well away from the plane in which the cuts should be made. Some fear that a stricture might develop at the level of the annular wound was seemingly unwarranted as there was no such tendency early or late.

REFERENCES

1. Caulk, John R.: Contracture of the vesical neck in the female. Jour. Urol., 6:341, 1921.
2. Caulk and Patton: Cautery punch for the removal of obstructive lesions at the vesical orifice in women and children. Jour. Urol., 33:504, 1935.
3. Fite, E. H.: Vesical neck obstruction in the female treated by resection. Urol. and Cutan. Rev., p. 163, (March) 1934.
4. Friedrich, H.: Sclerosis of the vesical sphincter in the female. Ztschr. f. Urol., 29:601, 1935.
5. Hicks, John B.: Bladder neck contracture in women. Surg. Clin. No. Amer., 14:1219, (Oct.) 1934.
6. Knorr, Richard: Contracture and sclerosis of the vesical neck in the female. Zentralbl. f. Gynäk., 51:1154, (May) 1927.
7. May, Ferdinand: Sclerosis of the vesical sphincter in the female. Ztschr. f. Urol. Chir., 42:308, 1936.
8. Nesbit, Reed M.: Vesical neck contracture in the female urethra with urinary obstruction. Urol. and Cutan. Rev., p. 291, (May) 1933.

9. PAPIN, M. M.: Disease of the vesical neck in the female. J. d'urol., 36:108, 1933.
10. PETILLO: quoted by Hinman. Principles and Practice of Urology, p. 449. Philadelphia: W. B. Saunders Company, 1935.
11. REES, C. R.: Prolapse of the gastric mucosa through the pylorus. Surg. Gynec. Obst., 64:689, 1937.
12. RICHER, M. V.: Suprapubic resection of the vesical neck in a woman. Bul. Soc. franc. d'urol., p. 194, (June 21) 1937.
13. THOMPSON, G. J.: Transurethral operation for the relief of dysfunction of the vesical neck in the female. Proc. Staff Meeting Mayo Clinic, 10:598, 1935.
14. VAN HOUTUM, G.: Six cases of chronic retention of urine in women caused by dysectasia of the bladder neck. Proc. Roy. Soc. Med., 28:1511, (Sept.) 1935.

ABERRANT URETERS ENDING BLINDLY

REPORT OF TWO CASES

WILLIAM J. ENGEL, M.D.

From the Cleveland Clinic, Cleveland, Ohio

The recognition of ureteral anomalies has increased with improved diagnostic methods until almost every conceivable type has been reported and many can no longer be regarded as rarities. A rather voluminous literature has accumulated which has been brought up to recent date in the articles which have appeared dealing with the various types encountered and, furthermore, almost every account reviews the embryologic development of the urinary tract which explains the occurrence of these anomalies so that to repeat it here would be an unnecessary redundancy.

The following cases are reported primarily because of their clinical interest, although in reviewing the literature I find them to be distinctly rare types. The general title of this paper covers both cases, but they represent two distinct types of anomalies and will, therefore, be presented and discussed separately.

Case 1.—This patient, a young housewife twenty-three years of age, was first admitted to the Cleveland Clinic Hospital in February, 1932, complaining of kidney trouble, attacks of chills and fever, and pain in the right side. The illness began ten weeks previously, at which time she experienced burning on urination without frequency or other associated symptoms. This was followed some days later by more marked dysuria, fever, and some pain in the right side. Since then, at frequent intervals, she had had a recurrence of a septic type of temperature which at times reached 104° F. and was associated with pain in the right flank.

One month previous to our examination, the patient had been admitted to another hospital where cystoscopic examination revealed a mild cystitis and urine secured by catheterization of the right kidney showed several pus cells. Culture of this urine yielded B. coli. A bilateral pyelogram made at that time showed a disproportion in the size of the kidneys, the left being larger than the right. The pelvis of the right kidney showed changes which were thought to be due to infection. A diagnosis of right pyelonephritis was made and improvement followed appropriate treatment which included one lavage of the kidney pelvis.

The symptoms recurred, however, and were similar to those ex-

perienced at previous attacks. When we first saw the patient her temperature was 100.4° F. Examination revealed no abnormalities except for definite tenderness in the region of the right kidney. Examination of the vagina and pelvis gave no significant findings. Examination of the blood showed 12,150 leukocytes and a specimen of urine secured by catheterization showed only three to five pus cells per high power field. Cystoscopic examination was carried out, no striking changes being seen in the bladder, and urine secured from the right kidney showed only 8 to 12 white blood cells, and culture yielded no growth of organisms. The pyelogram was repeated

Fig. 1. Case 1. Roentgenogram showing blindly ending ureter. The orifice is ectopic.

and showed evidence of ureteritis with an incompletely filled kidney pelvis. The diagnosis was still thought to be atypical pyelitis and ureteritis and, for the following four months, marked improvement followed treatment consisting of periodic lavage of the kidney pelvis and the administration of urinary antiseptics by mouth. The febrile attacks did not recur and the patient felt better and gained weight but continued to have mild pain on the right side and occasional burning on urination.

At this time, while attempting to catheterize the urethra, the patient experienced rather severe pain and the catheter would not enter the bladder. Investigation showed that the catheter had entered a previously unrecognized opening which was immediately below the

true urethral orifice and partially within the external meatus. This second orifice was somewhat reddened, tender, and edematous and some mucopurulent material could be expressed from it. Smears taken from this discharge showed Gram-negative intracellular diplococci. A probe could be passed through this opening for a distance of only about 4 cm.; however, a small No. 4 ureteral catheter could be passed somewhat higher but no urine or other secretion was obtained through the catheter. Ten cubic centimeters of skiodan were injected and a roentgenogram revealed the presence of a blindly ending ureter which extended upward on the right side and ended slightly

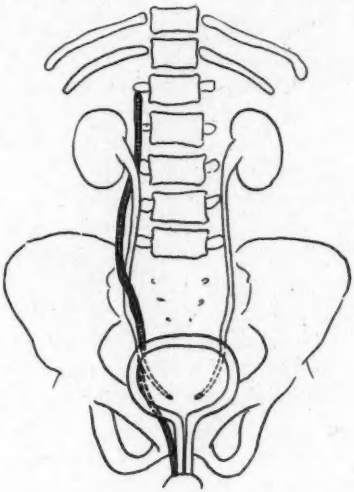


Fig. 2. Case 1. Diagrammatic drawing.

above the upper pole of the right kidney but apparently did not connect with the kidney substance (Fig. 1). Irrigation of the ureter with 0.5 per cent protargol and 1 per cent silver nitrate was followed by a rapid improvement and soon by complete cessation of all symptoms.

This patient has been seen periodically. She has since gone through two normal pregnancies, and has had no further symptoms.

After the discovery of this anomaly, the patient and her mother were carefully questioned regarding the presence of enuresis and incontinence during childhood. These questions yielded entirely negative answers. There had never been any urinary incontinence and the only significant statement was that at the time of birth there was

supposed to have been something extra in the vaginal region which a physician told them did not mean anything. With this history, one may conclude that there had never been any secreting renal tissue at the upper end of this ureter. Furthermore, in retrospect, it seems probable that all the symptoms were due to this infected, blindly ending ureter, and that the previous impression of a pyelitis of the right kidney was erroneous (Fig. 2).

In this case, a congenital anomaly assumed clinical importance because the ureter became infected. Had this not occurred, it is not unlikely that this patient might have gone through life without the condition being recognized as she had previously had no symptoms to indicate its presence.

This suggests a possible explanation, in part, for the rarity of reports in the literature of this type of case, for I have been able to find only two others, that of Spitzer and Wallin[10] in which the lesion was bilateral, and that reported by Kraft.[5] These cases differ from the one reported here in that both patients had complained of urinary incontinence or enuresis, although both authors insisted that the fluid which came from the ureter was not urine. In discussing the embryologic origin, Spitzer and Wallin reach the conclusion that in their case the anomaly was not really a ureter but a persistent Wolffian duct. Kraft gave support to this contention, for in his case the structure was removed at operation and histological examination of the specimen showed epithelium varying from columnar (intestinal type) epithelium to stratified transitional (as in the bladder), with gland-like structures in the submucosa. They believed, therefore, that it was not a ureter but an adult Wolffian body. The case which I have presented yields no evidence to support or deny this contention, which is chiefly of academic interest.

Case 2.—The patient, a young white woman twenty-nine years of age, was first seen in October, 1934, complaining of recurrent, severe attacks of vomiting, pain in the lower right part of the abdomen, angioneurotic edema affecting the lips and tongue, and loss in weight. The onset occurred six years previous to this examination when the patient had frequent attacks of vomiting associated with pain in the right side of the abdomen. After several such attacks, a diagnosis of chronic appendicitis was made and an appendectomy was performed in 1928. This resulted in partial relief of symptoms and for the following three years she had only an occasional mild attack. The symptoms then returned and she experienced the same episodes

of vomiting, followed by pain in the right lower quadrant. At times these attacks lasted two or three days, then gradually subsided. A particularly severe attack occurred two and one-half years previous to this examination and this was so prolonged that she was hospitalized and fluids had to be administered intravenously and by hypodermocylsis in order to combat the dehydration and toxemia. Six months later, another severe episode occurred and again she was taken to a hospital for parenteral administration of fluids. With this attack, some icteric tingeing of the scleræ developed and this led to the suspicion of gallbladder disease. Duodenal drainage was done without relief of symptoms and, finally, in November, 1932, a cholecystectomy and left salpingo-oöphorectomy were performed. This afforded absolutely no relief from her symptoms and she continued to have the alarming seizures of vomiting and pain in the right lower quadrant which were increasing in frequency and severity. Throughout her illness there had been no urinary symptoms nor did questioning elicit any. She had had numerous investigations and various therapeutic attempts but her trouble continued. When I first saw her she had been vomiting for almost two weeks and had lost 10 pounds in weight.

General physical examination yielded no definite diagnostic findings. The patient was rather pale and undernourished. Her weight was 95 pounds, the blood pressure 110 systolic, 70 diastolic. There was some tenderness to deep pressure in the right lower part of the abdomen but no masses were felt. Pelvic examination revealed no abnormalities.

Laboratory examinations likewise gave no significant findings. The urine was entirely normal, the blood count showed 4,400,000 red cells, 5,200 white cells, and 84 per cent hemoglobin. The blood chemistry was within normal limits and the blood Wassermann and Kahn tests gave negative reactions.

It was our opinion that the right urinary tract should be investigated and, accordingly, a cystoscopic examination was carried out October 26, 1934. The bladder was found to be entirely normal. The ureters were catheterized and some resistance was observed on the right side about 5 cm. from the meatus and, when passing this point, the patient complained mildly of the type of pain she had been experiencing. A roentgenogram showed no suspicious shadows in the urinary tract and the urogram gave normal findings except for small, almost infantile type of kidney pelves. Analysis and culture of the urine secured from the kidney was normal.

Because of the constriction in the ureter and the reproduction of pain, it was felt that this must be a ureteral stricture and ureteral dilatation was advised. The patient returned one week later for this service and, upon observing the bladder, a small fold was noted immediately below and medial to the right ureter. This had escaped attention at the previous examination. Although it did not have the typical appearance of a ureteral orifice, it was probed with a ureteral

catheter and found to be an accessory ureter. The smallest ureteral catheter would pass but 4 cm. and an attempt to pass it further caused severe pain which very accurately reproduced the pain of which the patient had complained. An attempt was made to inject skiodan for roentgenographic visualization but the injection of even two or three minims produced such excruciating pain that further attempts had to be discontinued. However, another catheter was passed up the normal right ureter and a roentgenogram made (Fig. 3).

Fig. 3. Case 2. Roentgenogram. The larger catheter has been passed to the kidney through the normal ureter. The smaller catheter has been passed as far as possible into the blindly ending ureter.

Having thus demonstrated the presence of an aberrant ureter, the exact reproduction of the patient's pain when instrumenting this ureter made me feel certain that here was the seat of the patient's trouble. I felt justified in advising operation to explore this ureter with a view to its removal. The patient was naturally loath to accept this advice because two previous operations had failed to relieve her symptoms, so she returned home. Within a few days, however, she had another extremely severe episode of vomiting and pain which she described as more severe than any other and as soon as she recovered she returned for operation.

The operation was carried out on December 24, 1934, spinal anesthesia being used. It had been planned to approach the ureter

extraperitoneally, but because of the previous operation, the peritoneum could not be reflected, so the ureter was exposed transperitoneally. The normal ureter was readily identified, as it contained a previously introduced ureteral catheter, and immediately medial and slightly posterior to the normal ureter, the second ureter was seen. It was about one-half the size of the normal ureter. An incision was made in the posterior peritoneum at the level of the brim of the pelvis immediately over the ureter. At this time very active peristalsis was noted in the aberrant ureter which continued throughout the operation. The aberrant ureter was then mobilized and separated from the normal ureter downward to the bladder and divided between clamps. On following this aberrant ureter upward, it was seen to cross the normal ureter anteriorly about an inch above the brim of the true pelvis and to pursue a course parallel and lateral to that of the normal

Fig. 4. Case 2. Photograph of specimen removed.

ureter. It was followed up as far as possible through this incision but the end could not be reached. Tape was therefore tied to the end and the ureter was tucked up behind the posterior peritoneum, which was then closed and the lower incision closed. Through a lumbar incision the ureter was again picked up and followed upward where it suddenly ended blindly at the lower pole of the right kidney. From the tip of the ureter numerous small filamentous bands, undoubtedly nerves, could be seen proceeding to the hilus of the kidney, apparently communicating with the renal plexus of nerves. Inspection of the kidney showed it to be normal in appearance except that it was unusually small. The ureter was removed and the incision closed with drainage. The patient had an entirely uneventful recovery from this operation.

Examination of the specimen removed (Fig. 4) showed a seg-

ment of ureter 20 cm. in length and varying from 3 to 4 mm. in diameter. The upper end terminated blindly and when fluid was injected under pressure, it was determined that no opening was present. There was a small, patent lumen which permitted the passage of a filiform bougie. Histologic examination of the cross section showed a tubular structure with a small patent lumen lined by a transitional type of epithelium such as that found in the normal ureter. Submucous, muscular, and adventitial coats were present.

The diagnosis was normal accessory ureter (Fig. 5).

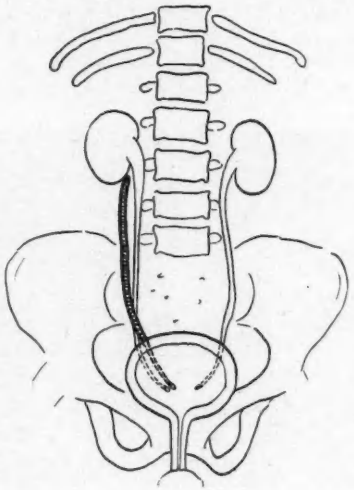


Fig. 5. Case 2. Diagrammatic drawing.

This patient has been seen at frequent intervals in the past three and one-half years. She has been entirely free from symptoms since the operation, she has had no recurrence of the pain in the right lower quadrant, and none of the nausea and vomiting of which she formerly complained. Soon after the operation she gained about 20 pounds in weight and this has been maintained throughout the past three and one-half years. It is also interesting to note that she has had no subsequent attacks of angioneurotic edema although I have no explanation for this.

A search of the literature reveals only five other cases resembling this one. Hanlon[8] reports a case found at autopsy which presented two ureteral orifices on each side in the bladder. On the left

side there was complete duplication of the ureters and kidney pelves while on the right a single pelvis and ureter drained into the upper orifice while the lower orifice ended in a blind pouch 3.8 cm. long, whose course was entirely within the muscular coat of the bladder. In Everett's[1] case, there was partial duplication of the left pelvis and upper ureter, while on the right side there were two ureteral orifices, the lower medial one ending blindly at a distance of 6 or 7 cm. No symptoms were attributable to it. In Furniss'[2] case, there was a supernumerary ectopic ureter on the right side with two intravesical orifices on the left, the lower ending blindly at a distance of 20 cm. It is interesting that attempted injection of this blind ureter produced severe pain, which coincides with my experience. In Lau and Henline's case, there were three ureteral orifices on the right side, one ending blindly and apparently producing no symptoms. Minder[8] found a single ureter and pelvis on the left side with two intravesical ureteral orifices on the right, the upper one apparently ending blindly at a distance of 20 cm. A review of this case leaves doubt that this was a true blind ureter as previous abdominal operation for supposed cholelithiasis had revealed a large, soft mass in the area of the right kidney, probably a large hydronephrosis of the lower pelvis, and the apparent blind ureter may simply have been a ureter which was completely obstructed. The cases of duplicate ureters ending blindly reported by Kretschmer,[5] Sisk and Kundert,[9] and Harris [4] differ from Case 2 in that only one ureteral orifice was present in the bladder, the ureter bifurcating above the bladder with one branch ending blindly.

I feel that interest in this case extends beyond the mere recording of another congenital anomaly. Here we have a perfectly normal, uninfected, unobstructed segment of ureter which conveys no secretion and yet is capable of producing severe pain and alarming reflex symptoms in the gastro-intestinal tract. The occurrence of gastro-intestinal symptoms due to lesions in the urinary tract is a matter of common observation, but in most cases the cause of the pain can usually be demonstrated clearly. I believe we have but one explanation of the pain in this case and that is hyperperistalsis (noted at operation) and/or spasm. If this can occur in such a ureter, is it not also possible for a normal ureter to behave in the same manner? If we assume an affirmative answer, one

has a much more real answer to many cases of so-called nephralgia and many, if not most, so-called ureteral strictures may be due to ureteral spasm. Nor is an affirmative answer unreasonable, its counterpart being seen in other smooth muscle, notably the intestinal tract, appendiceal colic, or even the coronary artery. I am certain many have encountered patients with typical pain in the kidney or ureter without demonstrable organic disease in the urinary tract, and I believe many of these cases may be due to ureteral hyperperistalsis or spasm. Wharton[11] holds a similar view and has recommended denervation of the ureter for its relief, reporting favorable results from this operation.

Furthermore, is it not possible that the ureteral stump left following nephrectomy might in the same manner be capable of producing pain? Occasionally a patient who has had a nephrectomy complains of pain in the groin or along the course of the ureter. We have never seen one of such severity as to justify ureterectomy, yet such an instance may arise. The question is presented for future experience to answer.

The cases presented here emphasize the importance of careful and complete investigation of all patients with obscure abdominal pain or gastro-intestinal symptoms, and serve as further examples of the frequency with which such symptoms are due to lesions in the urinary tract.

A supernumerary ureter without functional connection with kidney tissue, whether the ureteral orifice is ectopic or intravesical, may be easily overlooked. If an intravenous urogram or pyelogram reveals a congenital type of kidney, a more careful search for other developmental anomalies should be made. Intravenous urography is of neither positive nor negative value in the visualization of such ureters.

If the ureteral opening is ectopic, certain highly suggestive symptoms are usually present. The diagnosis should never be overlooked if dribbling of urine or a urine-like substance is present when the bladder is functioning normally. In Case 1 this symptom never appeared and in a true ureter ending blindly one would not expect it to appear. The symptom which was present, i.e., burning without associated frequency of urination, might have suggested the presence of an extravesical focus of irritation. Likewise, a history of prolonged irritation of the vagina in the absence

of a sufficient etiologic factor should lead to a most thorough visual inspection of the vaginal introitus, urethra, and cervix.

The recognition of intravesical supernumerary orifices should give no especial difficulty to the experienced observer. Inasmuch as they are occasionally encountered, he should systematically look for them whether or not their presence is indicated clinically.

The symptoms of supernumerary ureter may vary from those of infection and obstruction of any ureter to predominant disturbances in the gastro-intestinal tract as a result of nonobstructive, non-inflammatory spasm such as were encountered in our Case 2.

Until the possibility of this condition is kept in mind constantly and a systematic search made for such a condition, it is certain that the diagnosis may be missed and therapeutic efforts be futile.

REFERENCES

1. Everett, H. S.: Reduplication of renal pelvis and ureter. Jour. Urol., 36:1-21, (July) 1936.
2. Furniss, H. D.: Supernumerary ureters with extravesical openings. Jour. Urol., 37:341-360, (March) 1937.
3. Hanlon, F. R.: Rare anomaly of ureter. Jour. Urol., 21:123-127, (January) 1929.
4. Harris, A.: Ureteral anomalies with special reference to partial duplication with one branch ending blindly; report of two cases with renal obstruction cured by surgical resection. Jour. Urol., 38:442-454, (November) 1937.
5. Kraft, R. W.: Supernumerary ectopic ureter. Ann. Surg., 93:630-634, (February) 1931.
6. Kretschmer, H. L.: Duplication of ureters at their distal ends, one pair ending blindly; so-called diverticula of ureters. Jour. Urol., 30:61-73, (July) 1933.
7. Lau, F. T., and Henline, R. B.: Ureteral anomalies, report of case manifesting three ureters on one side with one ending blindly in aplastic kidney and bifid pelvis with single ureter on other side. Jour. A.M.A., 96:586-591, (Feb. 21) 1931.
8. Minder, J.: Double ureter. Ztschr. f. Urol., 19:680-683, 1925.
9. Sisk, I. R., and Kundert, R. R.: Duplication of lower ureter ending blindly. Jour. Urol., 38:261-266, (September) 1937.
10. Spitzer, W. M., and Wallin, I. E.: Supernumerary ectopic ureters. Ann. Surg., 88:1053-1062, (December) 1928.
11. Wharton, L. R.: The innervation of the ureter with respect to denervation. Jour. Urol., 28:639-673, (December) 1932.

TORSION OF THE APPENDIX TESTIS

(HYDATID OF MORGAGNI)

ALEXANDER RANDALL, M.D., F.A.C.S.

Philadelphia, Pennsylvania

This interesting clinical-pathologic entity is being presented for several reasons: First, to bring the reported cases up to date (end of 1937) since the excellent presentation of Dix in 1931; secondly, to include additional cases; thirdly, to try to correct the earlier statements that the lesion occurred only in childhood and adolescence; fourthly, to accentuate the varying pathology; and fifthly, because the American medical literature seems peculiarly silent on observations of the condition, whose prompt diagnosis and surgical treatment will save prolonged suffering.

HISTORY

Colt[3] is credited with publishing in 1922 the first accurate description of a case in which operation was performed; and his presentation immediately brought case reports from Shattock[29] and from Walton,[32] each of whom had operated upon such a patient in 1918 and 1913 respectively. Shattock's observation remains the only one where two hydatids on a single testis were each undergoing acute torsion. Ombridanne,[21] in 1913, also saw the lesion in his fifth reported patient, but confused the picture with torsion testis (of which he was writing), though he specifically stated that testicular torsion was not present in this case.

The constant publications of Mouchet[18, 19] since 1923 gave to him the credit for focusing attention on the clinical picture, the true pathologic change, the ultimate significance and the necessity of prompt surgical treatment. He has personally observed thirteen accredited cases (Dix).

In 1931 Dix[5] published all cases to the end of 1930, and tabulated forty-two cases then in the world's literature. He added three further cases where the clinical picture was similar, but the causative factor lay in torsion of other vestigial structures. To this total of forty-five he added his two personal cases (one vestigial) and six additional unpublished ones from Mouchet (per-

sonal communication), bringing the grand total to fifty-three, of which forty-nine were torsion of the appendix testis, and four of other vestigial structures as follows: two of the appendix of epididymis, one of the organ of Giraldes, and one of the vas aberrans of Haller.

The literature from 1931 to 1937, inclusive, I have found to contain seventeen reported cases of simple torsion of the appendix testis and one case of torsion of a cyst of the vas aberrans. This brings the total in the literature to seventy-one, of which sixty-six are true torsion of the hydatid of Morgagni (appendix testis) and five of other vestigial structures.

To this list I wish to add two cases of torsion of the appendix testis; so that the tabulation to date records:

Torsion of the appendix testis (Morgagni)	68
Torsion of the appendix epididymis	2
Torsion of the organ of Giraldes	1
Torsion of the vas aberrans	2
Total	73*

That there have been only two articles in the American literature, Foshee[8] (two cases) and Rhodes[24] (two cases), seems worthy of especial remark, and probably many have been unappreciated and simply considered epidido-orchitis of undetermined origin. Such is a pity, as prolonged, or recurrent, invalidism has been repeatedly observed and reported.

ANATOMY

Gross anatomy recognizes that the sessile hydatid of Morgagni is the most constantly present rudimentary structure of that group which owe their origin to vestigial remains of the Müllerian duct, or to embryonic faults of development. Situated on the anterior face of the superior pole of the testis, it lies free of the overhanging globus major of the epididymis. Paradoxically, it is more often pedunculated than sessile, and its proper title is the *appendix testis.*

The *appendix epididymis,* often called the *stalked hydatid,* is less constantly present, and arises from the tubules of the epi-

*In a brief discussion of both torsion testis and torsion of the appendix testis Sorrel[30] reports that he has observed seven cases of torsion of the hydatid of Morgagni and two cases of torsion of the organ of Giraldes, giving the ages from "four and one-half to thirteen years," but without recording any further data. Including these, as Dix did those of Mouchet, the grand total becomes eighty-two, with torsion of the appendix testis alone represented by seventy-five cases.

genitalis that do not form tubuli collectivi. It is said to contain plain muscle in its stalk.

The *paradidymis,* or organ of Giraldes, is composed of a group of rudimentary tubules within the structures of the first portion of the cord, and lesions therefrom appear separate from both the testis and the epididymis. These tubules represent embryonic remnants of the paragenitalis, or vestiges of the Wolffian body.

The *vasa aberrantia* of Haller are located in the middle of the epididymo-testicular groove, and are again embryonic elements that have failed to consummate their total development, and have their origin probably from the Wolffian duct.

It is of interest to recall that similar vestigial remnants occur in the female. An hydatid of Morgagni, properly termed the *appendix vesiculosa,* is found below the fimbriated end of the fallopian tube, but here it represents the vestigial remains of the Wolffian duct. Putzudonedder[23] presents a complete discussion of the anatomy and pathologic lesions of the female hydatid, while Henrich[14] reports a case of torsion in this hydatid and quotes three further cases from the literature.

Microscopically the hydatid of Morgagni is covered with simple cylindrical epithelium and is composed of loose fibrous tissue, with blood vessels and some plain muscle fibers, and usually there are found remnants of a duct (Müllerian), lined by ciliated epithelium,

PATHOLOGY

It is a bit confusing, as one reads the brief case reports, to classify each case clearly, and to determine whether torsion was present or not. To begin with, repeated attacks, with evidence of detorsion, have been recognized—Guillemin and Grandineau,[11] Roche,[25] Travernier and Garin.[31] This represents the "formes frustes" of Mouchet. Secondly, the term "infarction" is used—Guerin,[10] Blauchat,[1] Foshee[8]—a distinction one would consider difficult to make, even microscopically, after five days' duration, as in one of Foshee's cases. Thirdly, the diagnosis of fibroma has been given—Salmon and Contiades[28]—and, again fibroma of the hydatid *without* torsion—Salmon, Mosinger and Contiades[27]; Glass.[9] Cyst of the hydatid—Meyer-Wildisen[16]—6.5 cm. in diameter is reported. This confusion, however, is of academic inter-

CLINICAL FINDINGS

No.	Year of Publication	Observer	Age	Testis Affected	Duration	Physical Signs			
						Temp.	Local Condition		
							Appearance of Scrotum	Cord	Palpation of Testis
1	1931	Guilleminet	12	Left	Repeated attacks Many days	Normal	Normal	Normal	Tender at upper pole
2	1932	Foshee	16 mo.	Left	5 days	100	Double size and red	Slight thickening	Enlarged, firm and tender
3	1932	Foshee	8	Left	3 days	98.8	Swollen and red	Normal	Firm and tender
4	1933	Guillemin and Grandineau	10½	Left	14 days	39.5	Swollen	Normal	Swollen not tender
5	1933	Inouye	33	Left	....	39	....	....	Painful
6	1934	Chiariello	12	Left	1 day	37.4	Red and swollen	Normal	Swollen
7	1935	Blauchat	..	....	....	..	....	....	....
8	1935	Guerin	4½	Left	1 day	38.2	Swollen and red	Swollen	Tender
9	1935	Moncalvi	9	Right	3 days	..	Testis in canal	....	Tender—swollen
10	1935	Rhodes	39	Left	28 days	Normal	Swollen	....	Not palpable
11	1935	Rhodes	11	Left	2 days	100	Red and swollen	Normal	Very tender
12	1935	Roche	14	Right	2 days	99	Normal	Normal	Normal
13	1935	Rochet and Pouyanni	15	Right	3 days	..	Tender and unilateral swelling	....	Tender
14	1936	Grasso	11	Right	3 days	37.3	Edema and red	Thick and tender	Swollen and tender Epid. not enlarged
15	1936	Olascoaga	4	Left	4 days	Normal	Swollen	Normal	Double size
16	1936	Olascoaga	11	Left	7 days	Normal	Swollen and red	Very Painful	Enlarged
17	1936	Tavernier and Garin	13	Left	Repeated attacks	Normal	Slight edema	Normal	Tender
18	1938	Randall	34	Left	Repeated attacks 3 days	Normal	Normal	Normal	Tender
19	1938	Rosenblum	12	Right	3 days	99	Red and edematous	Normal	Tender at upper pole

OPERATIVE FINDINGS

OPERATIVE FINDINGS

No.	Observer	Day of Attack	Cord	Fluid Contents	Testis	Epi-didymis	Appendix of Testis			
							Size	Color	Turns	Direction
1	Guilleminet	Many days	Normal	Serum	Normal	Normal	Grain of Wheat	Ochre	Had detorsioned	....
2	Foshee	5 days	Edema	....	Normal	Edema	1 cm.	Blue-black	....	....
3	Foshee	3 days	Edema	Clear Yellow	Twice Normal	....	1 cm.	Blue-black	3	Clockwise
4	Guillemin and Grandineau	3rd attack in 14 days	Normal	Brown	....	....	8 mm.	Black	1½	Clockwise
5	Inouye	15 days	....	....	....	....	1½ cm.	Dark red	1	Clockwise
6	Chiariello	3 days	Normal	Slightly hemorrhagic	Enlarged	....	Pea	Black	....	....
7	Blauchat	....	....	....	....	....	....	....	....	....
8	Guerin	1 day	Congested	Hemorrhagic	Congested	Congested	1 cm.	Blue	....	....
9	Moncalvi	3 days	Congenital Hernia	Sero-hemorrhagic	Ectopic in canal	Edema	Small	Red	+	....
10	Rhodes	28 days	Normal	4 oz. hemorrhagic	Normal	Normal	3 cm.	Necrotic	....	....
11	Rhodes	2 days	Normal	Yellow	Normal	Normal	2½ cm.	Bluish	2	Clockwise
12	Roche	2 days	Normal	Yellow	Normal	Normal	....	Purple Red	2	Clockwise
13	Rochet and Pouyanni	3 days	Normal	....	Inverted	....	Cherry	Black	1	Counter-Clockwise
14	Grasso	3 days	Normal	Sero-hemorrhagic	Normal	Normal	Large pea	Black blue	+	....
15	Olascoaga	4 days	Normal	Amber	Double Normal	....	Enlarged	....	....	....
16	Olascoaga	7 days	Normal	Amber	Normal	Normal	Enlarged	Red	....	....
17	Tavernier and Garin	....	Normal	Sero-hemorrhagic	Normal	Normal	Double Normal	Violet	Many times	....
18	Randall	3 days	Normal	Amber	Normal	Normal	2 cm.	Red	1½	Clockwise
19	Rosenblum	3 days	Normal	Amber	Normal	Normal	Large pea	Deep purple	....	....

est only, and for the clinician the picture remains very much the same, and the therapy indicated is always operative interference.

It has been necessary to exclude from the series those cases which do not present acute torsion as the major clinical-pathologic condition, and to include only those where this factor of torsion is present, or where repeated attacks with detorsion have been recognized.

CLINICAL PICTURE

The clinical picture has some confusing points. The onset is practically always sudden, with unilateral acute pain. The pain is rarely so severe or so continuous as that accompanying acute infectious epididymitis, but palpation is distressing, and in children the pain is probably deceptively exaggerated. A confusing symptom is a concomitant redness and edema of the scrotum at the onset of the attack, and in children especially there is a slight elevation of temperature that makes one think of an infectious process. Ruling out a urethritis, mumps, tuberculosis, or other general disorders, clears this side of the diagnostic picture.

Complete torsion of the testis presents greater difficulty; though this condition is almost uniformly of greater symptomatic severity, and, fortunately, this differential diagnosis is not essential since prompt operative interference is the treatment of choice in both conditions.

In cases of a few days' duration the diagnosis becomes easier, and unless edema persists, or a secondary hydrocele collection interferes, the *spot tenderness* at the superior pole of the testis and just under the globus major of the epididymis is diagnostic. With rare exception, general systemic symptoms are absent, and though fever is usual at onset, chill, nausea, vomiting, etc., are rarely recorded. Inouye's[15] patient, who had fourteen attacks in sixteen years, is of interest, in that frequency of urination regularly occurred with each attack. Roche[25] likewise reports urinary frequency and the unique radiation of the pain down the thigh; while the case reported by Tavernier and Garin[31] was long undiagnosed, as his pain in numerous attacks was regularly across the lower abdomen, until the last one, when the testicular character of the pain was first recognized.

As Dix[5] says, when the condition is thought of, diagnosis presents no insuperable difficulties, and it has been made correctly and

without reserve in a number of the published cases. It is certain, however, that many cases of this lesion are unrecognized, and drag out a long and painful course before resolution and a natural cure occur.

Three cases in Dix' tabulation show the lesion in ectopic testes; and one in my tabulation (Moncalvi)[17] had both testes ectopic and palpable in the groins, with the right one involved in a torsion of the hydatid.

AGE

The early reports made the condition one of infancy, childhood and adolescence, and Mouchet[19] wrote in 1925, "I am unable to explain why torsion of the hydatid of Morgagni presents itself exclusively in the infant and adolescent." Probably the absence of infectious conditions of the genitalia in this young group brought the diagnosis more readily to mind. In Dix'[5] statistics twenty-seven of the forty-two cases (64 per cent) he collected from the literature occurred in boys between the ages of eleven and fourteen, and only three were past their twentieth birthday. The six cases of Mouchet[5] as yet unpublished were of unrecorded age. In my additional nineteen cases, three were older than twenty years. As changes prior to and at puberty are thought to influence this torsion, it would be proper to take those past sixteen years as a criterion; and this shows that in the total series of seventy-three cases eleven (15 per cent) were post-puberal.

ETIOLOGY

The cause is still unknown. Certainly infection plays no part. Trauma has been discussed; sudden or violent cremasteric reflex response suggested; but too many cases occur during ordinary play or occupation to allow such to stand. A few have occurred during sleep, as in torsion testis. It is suggested, apropos of the marked frequency during adolescence, that increased vascularity with testicular growth and development may play an important rôle. Certainly those in whom the hydatid has a greater pedicle development become potentially more liable; and Case 1 demonstrates this, in that the hydatid from the opposite testis was far from sessile.

CASE REPORTS

Case 1.—R. B., aged twenty-three, single, white, consulted me December 16, 1936, complaining of repeated attacks of acute left testicular

pain of only ten to fifteen minutes' duration. His first attack was three months before, on September 14, 1936, following a game of tennis, which he played in rather tight "shorts." He awoke at five o'clock the following morning with severe left testicular pain and a generalized ache over the entire lower left abdomen, with radiation down the left thigh. He consulted a physician at nine o'clock, who advised a suspensory, and his pain was gone by three in the afternoon.

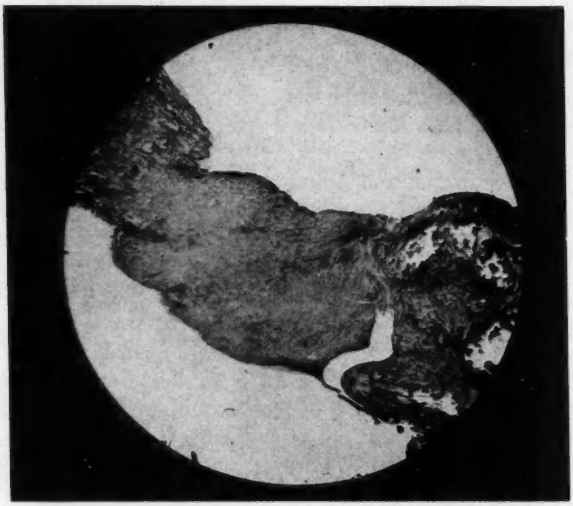


Fig. 1. Case 1. Microscopic section through the area of the pedicle of the left hydatid.

Since this primary attack he had worn a suspensory regularly, and has had but one other attack of moderate severity. At times exercise would develop an ache, and at others really strenuous exercise would cause him no discomfort. Long standing would cause an ache to develop, at times growing to be a constant annoyance. Three days before the consultation an attack of acute pain had lasted two hours, and then subsided entirely. He was otherwise enjoying excellent health, and planned to be married in three months. As his fiancée lived elsewhere, sexual excitement had played no part in the attacks.

An examination was completely negative: there was no pathologic change in the testis or the epididymis, and no hernia or varicocele. It was considered a case of torsion and detorsion of testis, and an operation for bilateral fixation was advised.

Operation was performed December 18, 1936, under gas anesthesia. Incision of right scrotum and testicular tunics (normal side). The

testis was delivered, and appeared normal throughout; except that the hydatid testis appeared double normal in size, 1.5 cm. long, and from its extremity there hung a gelatinous mass fully 1 cm. in length. This abnormality, which, of course, had been symptomless, was excised, and the pedicle cauterized with the high-frequency cautery. The wound was closed without drainage, after scarifying the testicular surface and taking two catgut sutures to include it while closing its tunica.

A similar scrotal incision was made on the left, where, on opening the tunica vaginalis, this startling picture was found: The stem of the appendix testis was fully 8 mm. in length, twisted one and one-half turns clockwise, and banded a dark red at the point of greatest constriction. Proximal and distal to this point many tiny cysts could be seen. Pendant from this twisted stem was a tongue-like gelatinous portion, fully 2.5 cm. in length and approximately 8 mm. in thickness. It hung so that its lower extremity was well below the middle of the testicular body. This was excised, and the wound closed without drainage, as on the opposite side. Cure has been permanent.

Microscopy.—Sections showed an organ for the most part devoid of its epithelial covering, though in a few places remnants were found, and consisted of low cuboidal cells occurring in single layers in some places, but in others two to three cells deep. Underneath the surface there was abundant stroma, composed of loose connective tissue which was in a state of fairly advanced degeneration, with only an occasional cell nucleus taking the hematoxylin stain. There was quite marked edema, and areas showing deposits of hemosiderin, indicating old hemorrhage. Only here and there were seen a few red blood cells lying in blood vessels with degenerated walls. There was some evidence of proliferation of fibroblasts and a few round cells. Scattered through the stroma were seen numerous tortuous, irregular spaces, whose walls contained large deposits of calcium salts, and whose lumina were for the most part empty, except for necrotic tissue and fragments of calcium deposition. These spaces might have been the remnants of ductal structures.

The picture suggests that this organ had been deprived of its normal blood supply for considerable time, and that the pathologic changes noted above were secondary to strangulation.

Case 2.—I wish to record this case, but as no operation was performed, verification is lacking.

A. B., aged thirty-four, married, white, asked me to see him at home in October, 1934. His history was that twelve days before he was suddenly seized, while at his desk, with acute right testicular pain. It was so severe that he was hurried home, and required morphia to quiet him. The following day it was still exceedingly tender on any motion, but eased under some local applications, plus heat. The day I saw him

he had been out of bed for the first time, and was quite comfortable with a supporter, though the testis was still sensitive to pressure. As four physicians had made four different diagnoses (epididymitis, hernia, gonorrhea and appendicitis), he was quite concerned about his condition, and feared that cancer was present.

An examination revealed a perfectly normal scrotum, testicle and epididymis; there was neither hernia nor history of urethritis. Palpating the right testis, one could feel with the greatest ease a small, firm mass, the size of a grain of wheat, on the anterior testicular surface just below the head of the epididymis. Pressure thereon reproduced identically the pain of complaint. Operation was advised, but declined when assured that it could not be cancer, and that in all probability the hyatid was then dead and would trouble him no more with acute pain.

*Case 3.**—A child, twelve years of age, was seen on February 10, 1938, three days after the onset of an acute painful swelling of the right scrotum and its contents, and with a temperature of 99°. An examination showed the swelling to be limited to the upper half of the scrotum and to the globus major of the epididymis. The scrotal skin was reddened, and palpation elicited acute pain. The cord was free of any involvement in the picture, and torsion was not demonstrable. Actually, the testicular body could be gently palpated without acute pain being elicited. A diagnosis of torsion testis was made, and immediate operation advised and accepted.

Operation was performed February 13, 1938, under gas anesthesia. An incision was made through the scrotal walls and tunica vaginalis, which exposed a normal testis and slightly congested epididymis. The hydatid of Morgagni was of a deep purple color, verging on gangrene, and the size of a large pea. It appeared stalked, with the distal two-thirds dry and verging on necrosis. No definite torsion was demonstrated, though looked for, but the appearance was so characteristic that it was considered that recent detorsion had occurred. It was excised, and no bleeding ensued. The wound was closed in layers with fine catgut. Recovery was prompt and cure established.

Microscopy.—The picture showed extensive hemorrhagic extravasation and quite generalized cellular necrosis.

TORSION OF OTHER VESTIGIAL STRUCTURES

In this period from 1931 to 1937, inclusive, the available literature contains two reports of this character:

Case 1 (Patch)[22]—Report of a case of torsion of a cyst arising from the vas aberrentia.

*Personal communication from Dr. Philip Rosenblum of Philadelphia, to be published later. The case was presented by him before the joint meeting of the Philadelphia and New York Urological Societies, April 21, 1938.

Case 2 (Sorrel)[30]—Report of two cases of torsion of the organ of Giraldes. (See footnote page 284.)

TREATMENT

The operation is so simple, and so devoid of any serious complications, that it should always be advised. As I was able to demonstrate so clearly, in my Case 1, the bilateral development of unusually long hydatids, it would seem advisable to operate on both sides in any given case. The fixation of the testis to the incision in the tunica vaginalis, when sewing up, I would likewise advise as a step to prevent subsequent torsion testis, as these two conditions have been reported as occurring simultaneously.

The question of conservative, non-operative treatment is ill-advised: Firstly, because no local treatment relieves the distress; secondly, because detorsion and recurrent attacks are possible; thirdly, because the non-operative recovery can take longer than the operative removal and convalescence; and fourthly, we have the suggestion of Contiades and Merigot,[4] who report two cases where they felt evidence existed that a hydrocele collection was secondary to a small foreign body found within the tunica vaginalis, and in each case the history gave evidence that torsion of the hydatid had preceded the development of the hydrocele.

CONCLUSIONS

1. Two additional cases of torsion of the appendix testis are reported; bringing the total to sixty-eight cases in the literature to the end of 1937. (See footnote page 284.)
2. It is of moment that only two American authors have reported cases.
3. It is assumed that the diagnosis is being missed, and masquerading under a faulty interpretation of the symptoms and signs.
4. Treatment is surgical and, as a preventive step, should be performed on both sides.

BIBLIOGRAPHY

1. Blauchat: Bordeaux Chir., 1935, VI: p. 159.
2. Chiariello: Pediatria, 1934, XLIV: p. 1104.
3. Colt: Brit. J. Surg., 1922, IX: p. 464.
4. Contiades and Mericot: Ann. d'Anat. Path. Med. Chir., 1932, IX: p. 795.
5. Dix: Brit. J. Urol., 1931, III: p. 245.
6. Dix: Ztschr. f. Urol. Chir., 1931, XXXIII: p. 486.

7. Dix: Ztschr. f. Urol., 1932, XXVI: p. 408.
8. Foshee: J.A.M.A., 1932, XCIX: p. 389.
9. Glass: Quoted by No. 27.
10. Guerin: Bordeaux Chir., 1935, VI: p. 157.
11. Guillemin and Grandineau: Rev. med. de l'est, 1933, LXI: p. 826.
12. Guilleminet: Lyon Chir., 1931, XXIII: p. 821.
13. Grasso: Arch. Ital. d. Chir., 1936, XLIII: p. 221.
14. Henrich: Amer. J. Obst., 1931, XXI: p. 121.
15. Inouye: Abst. Jap. J. Derm. & Urol., 1933, XXXIII: p. 47.
16. Meyer-Wildisen: Beitr. z. klin. Chir., 1936, CLXIV: p. 47.
17. Moncalvi: J. d'urol. med. et chir., 1933, XXXV: p. 501.
18. Mouchet: Presse med., 1923, XXXI: p. 485.
19. Mouchet: Bull. et mem. de la Soc. Nat. de Chir., 1925, LI: p. 431.
20. Olascoaga: Semana med., 1936, II: p. 1484.
21. Ombridanne: Bull. et mem. de la Soc. Nat. de Chir., 1913, XXXIX: p. 779.
22. Patch: Brit. J. Urol., 1933, V: p. 122.
23. Putzudonedder: Pathologica, 1937, XXIX: p. 98.
24. Rhodes: New England J. Med., 1935, CCXIII: p. 1005.
25. Roche: Clin. J., 1935, LXIV: p. 96.
26. Rochet and Pouyanni: Bordeaux Chir., 1935, VI: p. 135.
27. Salmon, Mosinger and Contiades: Ann. de Anat. & Path., 1933, X: p. 490.
28. Salmon and Contiades: J. d'urol. med. et chir., 1934, XXXVII: p. 412.
29. Shattock: Lancet, 1922, I: p. 693.
30. Sorrel: Bull. et mem. de la Soc. Nat. de Chir., 1935, LXI: p. 1270.
31. Tavernier and Garin: Lyon Chir., 1936, XXXIII: p. 598.
32. Walton: Brit. J. Surg., 1922, X: p. 151.

DISCUSSION

DR. CLYDE L. DEMING (New Haven, Conn.): May I ask Dr. Randall how old the oldest patient was?

DR. RANDALL: Forty-three.

DR. DEMING: I have seen several cases in the past, but I didn't know what they were. I must admit that I have learned something, and I appreciate Dr. Randall's paper.

DR. FLETCHER H. COLBY (Boston, Mass.): Dr. Randall, I feel, has rendered a distinct service in collecting these cases together in his clear, orderly way. It is a condition that has not been recognized here, as he says, as often as it has been in Europe.

One of these cases occurred at the Massachusetts General Hospital while I was on service and, as I remember, we were brave enough to make a definite diagnosis of torsion of one of the appendices.

I am also under the impression that several cases were reported from the Children's Hospital at Boston.

Another point is this: Do I understand that Dr. Randall thinks it is advisable to do a bilateral operation?

DR. WILLIAM F. BRAASCH (Rochester, Minn.): Obstruction of the bladder in the female, as reported by Dr. Neff, is certainly an interesting condition, and one which in recent years has been observed much more frequently. My colleague, Dr. Thompson, recently described some twenty-five cases observed at the Clinic during the last few years. It is caused more frequently by a hypertrophic condition of the sphincter than by prolapsed mucosa as described by Dr. Neff. Microscopic examination of the tissue removed usually shows sphincteric muscular tissue. It may be very difficult to determine sphincteric hypertrophy on cysto-urethroscopic examination, but it is recognized more easily by means of the direct vision endoscope than through a lens cystoscope.

I am under the impression that the operation can be done more satisfactorily by means of the punch operation, since it causes less destruction of underlying tissue than occurs with the loop. It has been our experience that tissue should be excised from several areas of the entire sphincteric circumference.

In several cases it was necessary to operate a second time because insufficient tissue was removed. Secondary atony of the bladder musculature is sometimes a factor in delaying recovery of bladder function and it may be weeks or months before the function is restored, even though sufficient sphincteric tissue is removed. Incontinence has occurred in several of the cases following the secondary operation, but it never remained permanently.

DR. AUSTIN I. DODSON (Richmond, Va.): I am very much interested in Dr. Neff's report, and I think it calls our attention to the importance of careful observation of the urethra as well as the sphincter area in these cases of bladder obstruction in the female.

I have seen three patients with obstruction at the neck of the bladder; the first was evidently a congenital condition inasmuch as the patient was a young woman who gave a history of dribbling and difficulty from birth. Neurologic examination gave negative findings and she was relieved by merely cutting through the posterior portion of the sphincter area with the Collins electrode.

The other two patients were elderly women who, while giving a history of frequency of urination for some time, had not known that they had difficulty in emptying the bladder until it was necessary for them to be confined to bed. One came into the hospital because of pyonephrosis with stone and complained of inability to void since she had been confined to bed. The kidney condition was treated. She was sent home with an indwelling catheter, which was to be removed in a short while. It was removed and had to be promptly reinserted. After six months of dilatation of the urethra and drainage of the bladder, she returned to the hospital and with the punch sections of tissue were removed from the posterior sphincter area, giving complete relief.

The other woman came to the hospital because of a gall-bladder condition and following the operation was never able to void. After remaining at the hospital about six weeks with every effort

at dilatation and irrigation, a similar punch operation was done which relieved her condition. In each of these cases there was fibrosis of the sphincter area with definite trabeculation of the bladder.

DR. NATHANIEL P. RATHBUN (Brooklyn, N. Y.): I just want to sound a warning about removing too much tissue in these cases of hypertrophy of the sphincter occurring in the female. This was illustrated in a recent case occurring in my clinic when one of my associates removed about a gram of tissue. This was followed by complete incontinence. A later plastic operation was unsuccessful so that she is still at the present time totally incontinent.

DR. RANDALL: To answer Dr. Colby: Is Foshee in Boston? Rhodes reports two cases and Foshee reports two cases. I think they are both from Boston. I don't want to overlook any case in the literature. I think the bilateral operation is indicated.

DR. COLBY: There is evidence enough of an abnormal appendix on the other side?

DR. RANDALL: There was in my one case.

HYPERTENSION IN DESTRUCTIVE INFECTED UNILATERAL LESIONS OF THE KIDNEY

E. GRANVILLE CRABTREE, M.D.

Boston, Massachusetts

There has appeared in the literature in comparatively recent times and from other than Urological sources, a series of studies which indicate a closer cause and effect relationship between urinary tract infection and hypertension than has been generally accepted (Loncope,[11] Butler,[4] Peters,[13,14,21] Weiss, Parker, and Robb,[20] Kinnelsteil and Wilson,[10] and others). It is to be noted that these writers indicate that the percentage of hypertension cases which show pyelonephritis at autopsy is very high, that the evidence produced is based on terminal findings either in end-result sick cases in medical wards or at autopsy, and finally that there are no data to indicate the relation of the infection-hypertension group to the whole group of pyelonephritis infections. The urologist who sees cases in which either spontaneous recovery of renal infection or cure under treatment takes place, has assumed a more optimistic point of view than is expressed by those who study end-results. The latter group, from entirely different data, has expressed pessimism about the significance of urinary tract infections which may prove to be an excellent warning to those who see the early stages of pyelonephritis, but which may apply to but a small percentage of the whole group of infections.

Until data are collected to indicate percentages of cases of renal infection which eventually develop hypertension, and whether or not certain degrees and types of infection are capable of producing hypertension either at the time of the infection or in subsequent years, urologists will be loath to accept the pessimism regarding the seriousness of all renal infections which is growing up rapidly in some non-urologic fields of medicine.

Three of my patients who have now been clear of infection for over one year after treatment with either mandelic acid or sulfanilimide, are known to have had bilateral renal infections for over twenty years without showing hypertension to date. All have been under observation for a period in excess of five years.

Four severe bilateral pyelonephritis in pregnancy cases have been re-examined after from eleven to sixteen years and found to be free from infection, hypertension, and evidences of renal insufficiency. Most urologists can probably duplicate or exceed this group from their experience. There are also under my charge both cases of pyelonephritis in pregnancy and cases of bilateral severe pyelonephritis in other conditions than pregnancy in which the infection is no longer present, and the patients have developed severe degrees of hypertension at the comparatively early age of forty years or less. We who deal with bilateral partial or completely obstructive infected lesions such as stone and hydronephrosis certainly do not find the majority of these patients exhibiting hypertension, even though the condition has been present for several years.

Urologists may well become interested and collect data on their infection cases in order that further light may eventually be thrown on the causal factors concerned. Attempts to unravel a terminal picture can at best be unsatisfactory.

There have appeared in the literature a few cases of unilateral urinary tract infection in which the patients have been cured of their hypertension, or markedly benefited, by removal of the infected kidney. Perhaps more such cases exist than I have been able to find. I have the impression that the phenomenon has attracted little attention and all have not been recognized. These cases are of particular interest because they are not terminal conditions, the specimens removed for study are surgical pathologic specimens and not autopsy specimens with terminal alterations, and the fate of the other kidney will in some, if not all, instances be determined eventually.

I have collected five cases of unilateral destructive renal lesions with hypertension in which the patient has improved after nephrectomy, and will add a sixth. The fifth case is also mine, although reported at a previous time because of interest in the lesion, an acquired stricture of the ureter, which appears now to have been responsible for the hypertension.

The first case, in regard to date, was reported by Quinby,[15] in 1923.

Case 1.—A boy of fourteen years, whose presenting symptom was headache of twelve months' duration, gave a history of scarlet fever,

appendectomy five years previous to entry, tonsillectomy ten years previous to entry, and operation for inguinal hernia two years previously. There had been nocturia for several years, usually once. There developed gradually about twelve months ago, headaches which were at first frontal, then also occipital. The boy had vomited at times for the past three months. Slight discomfort had been present in the right upper quadrant for quite some time.

Blood pressure was markedly elevated at 250 mm. of mercury systolic, 170 mm. diastolic. The urine showed no pus. Culture was not done. There were a few casts in the sediment. Specific gravity was 1010-1015. Phthalein test showed 15 per cent in two hours and ten minutes. Cystoscopy showed delayed excretion time, in 10 per cent in fifteen minutes after intravenous injection on the left. On insertion of the right catheter, there was no flow from the kidney and no injected fluid reached the pelvis. A palpable tumor of the right kidney was noted. At operation the mass on the right proved to be a tensely filled large hydronephrosis which was removed. Dr. Quinby has kindly supplied me with the pathologic report which was not included in the original report. For completeness it is here included with due credit given to Dr. Quinby for this added information as well as for the end-result note:

"Gross Description: Specimen consists of a right kidney, somewhat pyriform in shape and measuring 17x6 cm. in width at the upper end and 11 cm. at the lower, and 9 cm. in thickness. The fluid was removed by aspiration and the cystic kidney was filled with 10 per cent formalin and fixed in Kaiserling. On examination several days later, the outer surface of the kidney was pinkish grey and somewhat rough in appearance. The kidney contained about 500 c.c. of fluid. On section very little renal parenchyma is seen. The pelvis is dilated into a large cyst measuring approximately 8 cm. in diameter. Extending off this are five large calices measuring from 3 to 3.5 cm. in diameter. In several places only a shell of renal tissue exists and in no place is there more than 0.5 cm. of parenchyma. The pelvis is greyish pink and contains a few scattered, punctate areas of hemorrhage. About 4 cm. of ureter is attached to the pelvis of the kidney. This was opened and found to be patent throughout. It opened into the pelvis by a very small orifice which admitted a probe 1 mm. in diameter. The orifice in the pelvis is guarded by a small semi-lunar valve. It is readily understood how accumulation of fluid in the pelvis with distention closed off the ureteral orifice and eventually produced the hydronephrosis. Sections are taken for microscopic study.

"Microscopic Report: There are three sections. All show a diffuse destruction of the kidney. In one little area the histology of the tubules of the kidney can be recognized; otherwise the glomeruli and tubules are fibrosed. The larger vessels have their intima thickened. There is a diffuse, heavy lymphocytic infiltration.

"Diagnosis: Hydronephrosis; chronic pyelonephritis."

After the removal of the right hydronephrotic kidney, the blood pressure fell in the ensuing week to an average of about 130 mm. systolic, where it remained until discharge about a month after operation. During this postoperative period it became very evident that the suspicion entertained before operation of a very definite nephritis

in the active left kidney was confirmed and the boy was discharged to the nephritic clinic. The renal concentration test failed at any time to show a specific gravity higher than 1010 and the phthalein remained consistently low at approximately 20 per cent in two hours, the urea nitrogen in the blood being in the region of 46 mg. per cent.

The notes of the subsequent career show that the blood pressure rose again during the year following and that on the whole he did not follow the necessary limitation in diet except sporadically.

On September 28, 1924, the boy died following an operation for intestinal obstruction. At this time, however, the function of the remaining kidney was far from normal and a considerable degree of hypertension had returned although not so high as on the previous observation.

Case 2.—The patient, female, aged twenty-seven, had been previously reported by Crabtree.[5] She had scarlet fever and diphtheria in childhood; tonsillitis and rheumatism six years ago; appendectomy eight years ago; operation for tubal pregnancy four years ago and for ovarian cyst two years ago. In 1914, 1915, and 1917 she was delivered at term of normal babies. Operation for tubal pregnancy was performed in 1918. In 1919 there was a normal delivery. Micturition was never abnormal. In December, 1921, she entered the Boston Lying-in Hospital in early pregnancy with left costovertebral pain. The urine showed infection with a small trace of albumin. On January 10, 1922, symptoms of pyelitis in the right side appeared. She was studied at the Peter Bent Brigham Hospital. The left sediment findings were negative. The function of the kidney was 5 per cent in ten minutes after intravenous pyelography. The right kidney was infected. The organism concerned in the infection was Bacillus coli. Pyelography showed a normal left pelvis and ureter but a markedly dilated right renal pelvis.

In February, 1922, when now four and one-half months pregnant, the patient was re-examined by cystoscope at the Boston Lying-in Hospital. The right pelvis and ureter yielded 165 c.c. of purulent urine on suction. The left urine showed only bacilluria. In March, 1922, she was delivered by vaginal cesarean section for intractable right pyelonephritis. After delivery she improved steadily and was discharged from the hospital.

The patient failed to report until October 23, 1925, when six and one-half months' pregnant. The urine was infected and there were symptoms referable to the right kidney. Blood pressure readings were made daily for three days, October 23, 24, and 25, and at two hourly intervals, and ranged from 150 mm. systolic, 110 mm. diastolic the first day, to 120 mm. systolic, 72 mm. diastolic to 132 mm. systolic, 84 mm. diastolic (Chart I). She showed phenolsulphonephthalein test of 40 per cent in two hours and a small amount of albumin.

The patient was readmitted to the hospital November 24, 1925, for symptoms of toxemia. Blood pressure readings are shown on Chart II. Cystoscopic findings on admission showed right pelvic content of 60 c.c. of urine which was loaded with pus and cocci and bacilli. The phthalein function had an appearance time of four minutes and 14 per cent output in fifteen minutes on the left. There was no pelvic residual. The sediment showed a few pus cells and many

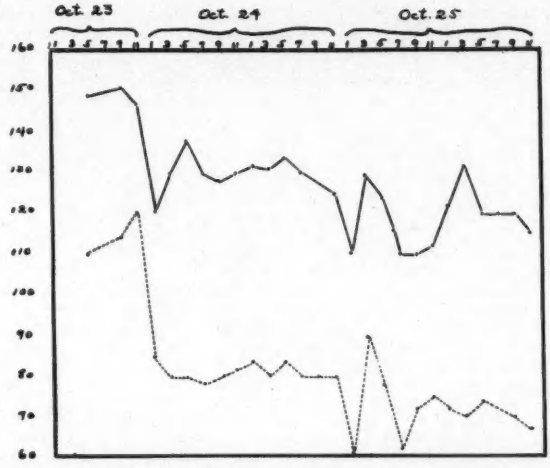


Chart I. Case 2. Two hourly blood pressure readings, October 23-25, 1925. Discharged undelivered, November 5.

bacilli and cocci. Only a right pyelogram was done. The pelvis was markedly dilated, as was the ureter, with dilated calices which showed much clubbing. Abdominal cesarean section and sterilization were done.

On January 8, 1929, she reappeared in the out-patient department clinic complaining of pain, of very recent occurrence, in the right kidney region. This kidney was palpable. The bladder urine was very cloudy with pus and the systolic blood pressure was recorded at 200 mm. of mercury. Cystoscopy showed 52 c.c. residual urine on the right, no residual urine on the left. There was no evidence at this time of ureteral narrowing on the right.

From December, 1926, to February, 1927, systolic blood pressure readings ranged from 180 mm. to 210 mm. The right renal pain continued. During this time five cystoscopic dilatations of the now narrowed right ureter were done with only temporary relief. During this period the function of the right kidney decreased, the urine remained infected, and there was only a trace of phthalein excretion.

The left kidney recovered from its bacteriuria and showed a phthalein output of 45 per cent in dilution of 250 c.c. in fifteen minutes. Pyelography showed that a long stricture had developed in the upper third of the right ureter. The cortex seemed thinned.

Nephrectomy was done. Pre-operative systolic blood pressure readings, two in number, made when resting in bed, were 180 mm. and 200 mm. One postoperative record was made on the twenty-first day of convalescence which read 120 mm. systolic, 76 mm. diastolic.

Dr. Tracy Mallory's report on the gross and microscopic examination of the specimen is as follows:

"April 7, 1927. Right kidney (nephrectomy following pyelitis of pregnancy). Weight 130 grams. Dimensions 10 by 5.5 by 4 cm. The kidney is shrunken, firm, and decolorized by the fixative. The capsule seems to have stripped readily, leaving a smooth, somewhat mottled surface. At the upper pole there is an irregularly shrunken, puckered area, darker in color, suggesting a previous inflammatory process. Several smaller puckered areas, about 1 cm. square, are seen on the outer border of the kidney.

"The renal pelvis and upper ureter are dilated, and about 4 cm. below the pelvis there is a definite ureteral stricture extending for about 3 cm. In this area the walls are hypertrophied three or four times the normal, and the ureter below this point still appears somewhat dilated.

"On cut section the calices are dilated and the walls of the pelvis thickened. The renal parenchyma appears fairly normal. There is no gross evidence of inflammation or necrosis. Sections taken as follows: (1) Kidney through shrunken area described above. (2) Kidney apparently normal, at the upper pole. (3) Kidney, apparently normal, lower pole. (1) Ureter below stricture. (2) Ureter through stricture. (3) Ureter above stricture.

"Microscopic examination of sections through unscarred areas of cortex and pyramids show that the glomeruli are uniformly slightly distended. In many instances the capsular space is obliterated, in others the narrowed space is filled with albuminous material. One or two capillaries of the glomerular tuft in almost every instance are occluded by masses of endothelial cells. Occasionally a polymorphonuclear leukocyte is present. In general the lining cells of Bowman's capsules are entirely involved in the process. Occasionally a desquamated cell is seen in the capillary space. The convoluted tubules are filled with albuminous material. The fixation is too poor to permit an accurate decision as to vacuolization or albuminous degeneration.

"Sections through a large scarred region show a wedge-shaped area with apex towards the pyramid. The tubules have almost entirely disappeared and a dense infiltration with lymphocytes and plasma cells replaces them. The tissue is shrunken and the larger blood vessels are drawn closely together. Many of them show considerable thickening of the intima. The glomeruli in this area are to a large extent completely sclerosed. The remainder show marked capsular thickening and adhesions between tuft and capsule.

"Sections of the ureter above and below the point of stricture show moderate thickening of the wall, a normal mucous membrane, and a slight degree of infiltration with lymphocytes and plasma cells. Section at the point of stricture shows a marked chronic inflammatory process. There is dense infiltration with lymphocytes and plasma cells of submucosa and muscularis, and considerable increase in fibrous tissue, bands of which run between, and split widely apart, the muscle bundles of the muscularis. The mucous membrane over this area is less regularly stratified than elsewhere and shows small papillomatous projections.

"Diagnosis: Chronic pyelonephritis, subacute glomerulonephritis, inflammatory stricture of the ureter.—(Signed) Tracy B. Mallory."

The systolic blood pressure fell from 200 to 210 mm., to 124 to 140 mm. in the weeks following the operation, and remained low in spite of the patient's resumption of the care of a house and six children.

Subsequent History.—Gall-bladder disease developed in 1927. One record of systolic blood pressure of 190 mm. was recorded during an attack of pain. The pressure soon returned to 145 to 160 mm. The

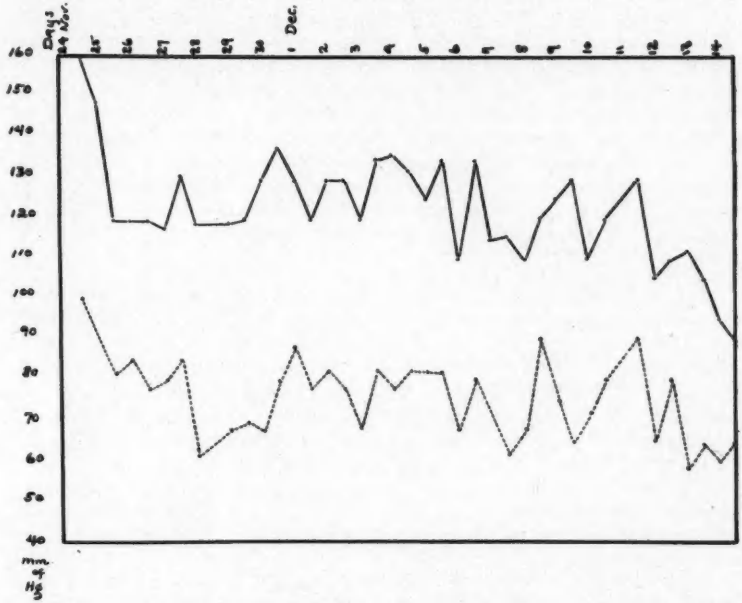


Chart II. Case 2. Blood pressure, November 24-December 14, 1925. Note: Cesarean section and sterilization were done, November 29.

urine showed no albumin, no sugar, no pus, bacteria, red cells, or casts. In March, 1929, the urine still showed no albumin. Tonsillitis had become troublesome. Non-protein nitrogen was 30 mg. per cent. She had gained a lot of weight to 210 pounds. Blood pressure was 140 mm. of mercury systolic, 74 mm. diastolic. Two-hour phthalein function was 39 per cent. In January, 1933, non-protein nitrogen was 25 mg. per cent. Urine showed no albumin, blood pressure 145 mm. systolic, 90 mm. diastolic. She had been working as a cook, and had been in excellent health.

The patient was seen again in April, 1938. She had had to give up work ten weeks before because of nervousness, bad headaches, and crampy pains in her legs. She is now short of breath and tires easily. There is nocturia five or six times. There have been specks before the eyes for about one year. On the whole, she had felt well up to the time she was forced to stop working. Weight is now 223¼ pounds. The urine is clear, dilute, but shows a trace of albumin. Sugar is absent. Specific gravity on four specimens ranges from 1.012 to 1.014. There are no casts in thirty fields. No pus, red cells, or bacteria can be seen. Culture negative. pH test was 5.5 to 6. Intravenous phthalein test shows, in four fifteen-minute excretion periods, 15 per cent, 30 per cent, 15 per cent, and 10 per cent in 500 c.c. dilution. Non-protein nitrogen is 26 mg. per cent. Intravenous pyelography shows a large, nondistorted, normal appearing kidney on the left. The right is absent. Dye appeared fairly promptly at five minutes after injection. The best plate was at fifteen minutes after injection of the dye. The calices, pelvis, and ureter seem normal. Blood pressure readings after activity are 196 mm. of mercury systolic, 124 mm. diastolic, and after resting, 190 mm. systolic, 122 mm. diastolic.

Case 3 (Butler's case[4]).—November, 1934. The patient, male, aged seven, had a presenting symptom of hematuria. The boy was healthy and had no past history of illness except minor children's diseases. Blood pressure on admission was 98 mm. of mercury systolic, 50 mm. diastolic. The urine contained a slight trace of albumin and was full of blood. X-ray showed a right renal calculus in a considerably dilated pelvis with blunted calices. The calculus later moved into the right ureter. The left kidney, pelvis, and ureter were normal. Non-protein nitrogen was 20 mg. per cent. Intra-muscular phenolsulphonephthalein was 30 per cent in the first hour and 25 per cent in the second hour. Ureterostomy for stone was done. By January, 1935, the urine contained pus, and culture showed Bacillus coli. On April 5, 1935, a nephrostomy was done on the right kidney. The fat was found to be abnormally adherent about the lower pole of the kidney and there were several aberrant vessels which did not appear to compress the ureter. The pelvis and ureter were greatly dilated. The renal cortex was much thicker than anticipated. Phenolsulphonephthalein test showed 15 per cent excretion from this kidney in the first hour and 10 per cent in the second hour. The catheter was removed April 30 and the patient was sent home with pyuria still present.

In August the patient returned to the hospital with cyanosis and dyspnea and rapid pulse rate. The liver was enlarged and there was dependent edema. The heart was enlarged. Blood pressure was 130 mm. of mercury systolic, 100 mm. diastolic. After digitalization, the pulse rate dropped to normal, the edema disappeared, but the blood

pressure rose to 160 mm. systolic, 105 mm. diastolic. The urine from the right kidney continued to show pus and Bacillus coli. The excretion of phenolsulphonephthalein had fallen to 3 per cent in one hour. The left kidney gave 16 per cent excretion and showed no organisms on culture. The urine concentration test gave specific gravity as high as 1.024. The non-protein nitrogen was 24 mg. per cent. During seven weeks' observation, the blood pressure varied between 122 mm. and 168 mm. systolic, and 90 mm. and 110 mm. diastolic. Nephrectomy was done.

The pathologist's report showed the following cortical findings in the gross. The capsule of the kidney was opaque, thick, and in certain areas markedly adherent to the kidney surface. Over the lower pole there was a large, irregular, slightly depressed dull purplish area to which the capsule was markedly adherent. At the superior pole were smaller discrete areas. The kidney was moderately firm but boggy and with poorly defined cortical and medullary zones. At the superior pole there was a wedge-shaped lesion with a red central area extending to the tip of an inferior calix.

The pelvic and ureteral dilatations were noted.

Microscopic sections showed the following changes in the cortical tissues: There was thickening, edema, and lymphocytic infiltration of the capsule. The interstitial tissues were densely infiltrated with lymphocytes, polymorphonuclear leukocytes and mononuclear cells. In occasional areas the renal parenchyma was replaced by polymorphonuclear leukocytes and lymphocytes. In other areas lymphocytes were packed densely, suggesting a lymph follicle. Inflammatory changes extended throughout the entire kidney. The convoluted and collecting tubules were dilated. Occasional tubules were filled with polymorphonuclear leukocytes. In many glomeruli there was increased prominence of the basement membrane both in the capillary loops and in the capsule itself. Many glomeruli were practically bloodless. Inflammatory cells in the glomeruli were lacking. Moderate thickening of both the media and intima of the smaller arterioles was noted.

After operation the blood pressure fell to 100 mm. of mecury systolic, 70 mm. diastolic; and the urine became clear. Six observations during the subsequent twenty months showed the heart to be of normal size, the urine negative for pus and bacteria, and the blood pressure never higher than 115 mm. systolic, 75 mm. diastolic.

Case 4 (Barney's case[8]).—A girl, ten years of age, with a history of pyuria of at least two years' duration was seen in March, 1937. There were pus and bacilli in the urine. There was hypertension of 190 mm. of mercury systolic, 120 mm. diastolic. The non-protein nitrogen and phenolsulphonephthalein were within normal limits. Right nephrectomy was done. The day following operation the blood pressure fell to 110 mm. systolic, 70 mm. diastolic, and remained below that level during the subsequent stay in the hospital. Three months

later the child was healthy and active with blood pressure reading at 92 mm. systolic, 60 mm. diastolic.

The kidney was described as small, irregularly scarred, with dilated pelvis. On section there was marked thickening of the media and intima of the arterioles. There was cell infiltration in areas throughout the parenchyma.

In a personal communication Dr. Barney reports that the child is still possessed of normal blood pressure after fifteen months from the date of operation. He, himself, will eventually present a more detailed report of this case.

Case 5 (Barker and Walters[2]).—February, 1938. The patient was a male, aged 42; presenting symptoms: increasing nervousness, some shortness of breath, and occasional mild morning headache all of approximately one year duration. The past history included appendectomy sixteen years before entry to the hospital, and cholecystectomy five years previously, at which time no gall stones were found. Twelve years previous to entry he had right renal colic with hematuria. There were several similar attacks six years ago and four years ago. In such an attack four years ago, 1933, chills and fever occurred. A large stone was found in the mid-portion of the right ureter. There was definite hydronephrosis and hydroureter above the stone. Ureterolithotomy was done, but the urine remained infected and the ureter could not be catheterized to the pelvis because of obstruction.

Roentgenograms in 1933 showed the right kidney to be of normal size, but hydronephrosis was present.

Roentgenograms in 1935 showed the right kidney to be moderately contracted.

Roentgenograms in 1937 showed the right kidney to be markedly contracted.

The patient had been told that all early examinations had shown that all tests on the left kidney had been normal and that numerous blood pressure tests over the previous ten years had been normal. He passed insurance tests in 1936, but in August, 1937, blood pressure readings showed 200 mm. of mercury systolic, 140 mm. diastolic.

The chief findings on physical examination were that there was sclerosis of radials and temporals. Blood pressure readings were 232 mm. systolic, 135 mm. diastolic; 170 mm. systolic, 120 mm. diastolic; 200 mm. systolic, 140 mm. diastolic; 180 mm. systolic, 125 mm. diastolic; 238 systolic, 150 mm. diastolic; and 240 mm. systolic, 146 mm. diastolic. After nine grains of amytal the blood pressure readings were 136 mm. systolic, 100 mm. diastolic; and 134 mm. systolic, 90 mm. diastolic.

On cystoscopic examination it was not possible to pass a catheter into the right ureter in its upper portions. Excretion of indigo carmine from the right side was Grade 2 and from the left Grade 3.

There were no bacteria found in either kidney urine, but Escherichia coli, micrococci, and pseudomonas were found in the vesical urine.

At nephrectomy a contracted kidney about one-third to one-half normal size weighing 48 grams was found. It showed a dilated pelvis, was nodular and showed small chronic abscesses.

Histologic examination showed that the cortex consisted of alternate portions of fairly normal renal tissue and areas where the parenchyma had been destroyed completely. Replacement by fibrous tissue and lymphocytic infiltration characterized these areas. Arcuate and interlobar arteries showed markedly thickened walls.

Three hours after operation the blood pressure was recorded at 230 mm. systolic, 140 mm. diastolic. From then on to the eleventh day the readings were irregular, but showed a gradual decline to 140 mm. systolic, 100 diastolic. After being allowed up for nine days and six days after leaving the hospital, he showed the following: after lying recumbent for eight hours the readings were 128 mm. systolic, 90 mm. diastolic; and 144 mm. systolic, 100 mm. diastolic, with a mean level of 135 mm. systolic, 95 mm. diastolic. Two months after operation pressure averaged 130 mm. systolic, 90 mm. diastolic.

Case 6.—A man, aged forty, gave as his chief complaint, loss of strength. The patient had childhood diseases but not scarlet fever, and had influenza once. There was repair of hydrocele some years ago. There were no other illnesses of any kind until two years ago. At that time while in Canada the patient suddenly developed a high fever with temperature of 103°, pain over the right kidney, which radiated down over the right thigh. He was taken home to Attleboro, Massachusetts. After about one month a diagnosis of perinephritic abscess was made, and the abscess was drained surgically. After the operation the patient remained in the hospital for five months, during which time nineteen other abscesses developed, chiefly in muscles of the abdomen, buttocks, thighs, and intercostal regions. All were drained. One has failed to heal. This is situated on the left chest wall. There is a shallow sinus which overlies a rib. During this long illness he lost a great deal of weight, was frequently transfused, but eventually recovered. The urine remained cloudy. After two years, his skin is unhealthy and blotchy, there is a small furuncle on the nose, and epidermophytosis of the hands. He has been unable to work on account of weakness. There is some frontal headache. At the end of his stay at the hospital he was well along the road to morphine addiction but recovered within the first year after operation. Mandelic and prontylin therapy had been tried and had failed to cure his condition.

Examination showed him to be a healthy looking male. Reflexes were normal, pupils reacted. Upper teeth were false, lowers well cared for. Tonsils were large but showed no pus. Over the left precardial area there was a tiny sinus which was dry at the time of

the examination. Moderate sclerosis of the radials was noted. The blood pressure was variable. At home, and when first seen in my office, his range on three determinations varied from 160 mm. of mercury systolic to 170 mm., and the diastolic has been above 100 mm. of mercury. The reading obtained when first admitted to the hospital while lying quietly in bed was 160 mm. of mercury for systolic and 120 mm. for diastolic. For the remaining blood pres-

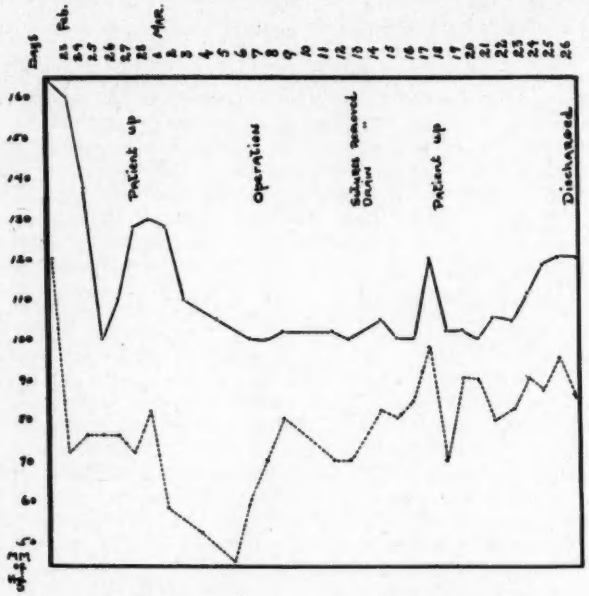


Chart III. Case 6. Blood pressure during hospitalization.

sure readings see Chart III. There was very slight edema of one ankle on admission.

The patient showed the following laboratory findings: red cell count 5,130,000; white cell count 17,400; polynuclear cells 66 per cent, lymphocytes 22 per cent, eosinophils 10 per cent, basophils 4 per cent. Many eosinophils showed vacuoles. The red cells appeared normal. The urine was cloudy, pH 5, albumin small trace, specific gravity 1.016 to 1.028. Sediment showed much pus, no casts. Stained sediment showed only staphylococcus. Culture, Staphylococcus albus. Non-protein nitrogen: 50 mg. per cent. Fasting blood sugar 76 mg. Blood Hinton test reactions were negative. Phenolsulphonephthalein test for two hours and ten minutes showed in

the first hour 25 per cent and in the second hour 25 per cent. Intravenous phthalein showed 10 per cent for the first fifteen minutes, then 15 per cent, 5 per cent, and 5 per cent for succeeding periods. Intravenous pyelography had been done at home. He exhibited the plates. The left kidney showed normal appearing cortex and the calices, pelvis, and ureter were entirely negative. The dye appeared at five minutes with the best plate at ten minutes after injection. The dye was cleared from the kidney except for faint traces about the pelvis in thirty-five minutes. On the right the cortex seemed very much decreased in size. There was a moderate hydronephrosis with obstruction just below the pelvis. The best plate was at twenty-five minutes after injection. The dye had not cleared at thirty-five minutes. There was prostatitis, chronic in type to palpation, with no increase in size of the gland, but nodularity. The prostatic secretions showed 10 to 12 pus cells, per high power field. Stains for bacteria demonstrated a moderate number of staphylococci.

Cystoscopic examination showed slight dulling of the mucous membrane of the bladder and redness about the prostatic urethra and trigone. Both ureters could be catheterized to the pelvis. There was very cloudy urine on the right side and clear urine on the left. Culture from the right showed Staphylococcus albus, from the left no growth. Blood culture showed no growth, after 120 hours. Sediment from the right showed pus. No casts were found. There was no excretion of phthalein after intravenous injection. On the left the excretion was 15 per cent in fifteen minutes. The sediment was negative. Stained sediments revealed no organisms.

Retrograde Pyelography: The kidney shadow on the right was incompletely visualized but seemed small. Following injection there was seen a moderate dilatation of the pelvis and major calices. The minor calices were still well cupped, and there was a definite zone of parenchyma outside the minor calices, varying up to a centimenter and a half thick. Following withdrawal of the catheter the ureteropelvic junction was seen sharply demarcated. The ureter was well outlined and smooth and showed no evidence of calculi.

Impression: Moderate hydronephrosis, right kidney, with partial obstruction at the uretero-pelvic junction which, in view of the history, might be due to adhesions rather than to aberrant vessel or band. The apparent smallness of the kidney might be due to rotation.

During the ten-day period of study at the hospital, the patient remaining in bed, the non-protein nitrogen readings were 50 mg. per cent, 35 mg. per cent, and 29 mg. per cent. Both systolic and diastolic blood pressures fell as shown in Chart III. Previous to the operation he was allowed up out of bed for three days. During this time there was a rise of systolic blood pressure of 30 points and the non-protein nitrogen to 48 mg. per cent.

Nephrectomy was performed, reported as follows:

"There has been a perinephritic abscess and the kidney was bound down by dense tissue. It was eventually freed and nephrectomy successfully performed. The obstruction to the ureter was due to scar tissue entirely. The wound oozed from the muscle and skin layers but there was very little oozing from the bed from which the kidney was removed. When sectioned the kidney was almost entirely a fat replacement, scarred, contracted, and showed much evidence of sepsis. In one end (the lower pole), it was infarcted."

Pathologic Examination: The specimen consisted of a thinly encapsulated gray nodule 1 cm. in diameter, surrounded by a small amount of fat. Cut surface was mostly gray and homogeneous with pinkish gray, irregular centers. There was also a previously opened kidney with perinephric tissue. Kidney, measuring 9.5 x 5.5 x 2.5 cm., weighted 70 grams. Capsule stripped with difficulty and was adherent by dense fibrous tissue in placees. Underlying tissue was hemorrhagic in upper pole. Previously cut surface showed poorly demarcated cortex and medulla. Cortex measured 0.4 cm. in thickness. Cortex and medulla showed foci of light gray to light green, thinly circumscribed, which when compressed exuded purulent material. Pelvis contained two irregular, soft, brown stones, each about 0.5 cm. in greatest diameter. Pelvis was slightly dilated. Pelvic mucosa was gray and smooth.

Microscopic Examination: There was marked reduction in the amount of renal substance and the whole kidney was so heavily involved by pyelonephric abscesses that it was difficult to make any definite statements with regard to it. However, there were occasional sclerosed glomeruli and some of the larger arteries showed fibrous thickening in their walls bringing them up to perhaps half again normal thickness. In one focus in the cortex there was marked thickening of a small artery by reduction of lumen to one-third. The renal tissue adjacent to this showed marked fibrosis and contracture, with numerous, partially sclerosed glomeruli. While there was lymphocytic infiltration present this was in all probability due to the associated pyelonephritis.

Microscopic Diagnosis: Acute and chronic pyelonephritis, chronic ureteritis, nephrolithiasis, hyperplasia of lymph node.

Following operation convalescence was uneventful. The wound healed by first intention. During his bed convalescence systolic pressure remained from 100 mm. to 110 mm., diastolic 70 mm. to 80 mm., except for one rise to 120 systolic, 98 mm. diastolic. After he regained his feet, systolic pressure did not exceed 120 mm., but diastolic pressure ranged from 80 to 94 mm. Discharge urine showed rare white cells, no albumin, and on forced fluids the specific gravity was 1.008. Non-protein nitrogen was 29 mg. per cent. At the end of two months after operation, the patient has gained 10 pounds, eats and sleeps well, and is never tired. His blood pressure is 128 mm.

systolic, 76 mm. diastolic. The urine is sparkling and clear with no sugar and no albumin. Specific gravity is 1.010-1.028. Sediment shows epithelial cells, 0-1 white blood cells. Stained sediment is negative for bacteria. Intravenous phenolsulphonephthalein test showed a slight trace the first fifteen minutes, then 12 per cent, 25 per cent, and 20 per cent in the ensuing fifteen minute periods, totalling 57 per cent in the first hour.

DISCUSSION

From a survey of the data pertaining to this small group of cases, one may conclude that the term "cure" after surgery should be used with reservations. While in three cases (Cases 3, 4, and 5) the data seem to indicate complete recovery for periods as long as two months, fifteen months, and twenty months, in the other cases (Cases 1, 2, and 6), return of hypertension is known to have occurred in two, and there is no certainty about the freedom of the remaining kidney from permanent damage at the time the surgery was performed (Case 6). In Case 1, the remaining kidney was recognized as nephritic at the time of surgery. In Case 2 there had been toxemia during one of the pregnancies and after eleven years the hypertension had returned at the age of thirty-eight years, and in Case 6 the variation in non-protein nitrogen previous to surgery is probably significant. Yet even in the nephritic case (Case 1) temporary relief from marked hypertension resulted, and in Case 2 relief from symptoms for ten years was obtained.

It is not easy to offer adequate explanations as to the mechanism of the hypertensions noted in these cases which will admit of such prompt decline in blood pressure following extirpation of the diseased kidney, on pathologic grounds. Vascular spasm which would persist over periods as long as symptoms were known to be present in some of these cases is improbable, although certain known facts suggest the possibility. Goldblatt[7] has shown that hypertension produced experimentally in animals may be allowed to persist for months and that the blood pressure will be capable of returning to normal after restoration of normal renal conditions. A pressor substance which is elaborated by the kidney, forced into the circulation constantly during the existence of the lesion in the human, and removed entirely at the time of nephrectomy, or in animals at the time the normal renal condition is

restored, is also a probable explanation. This substance could affect both the changed remaining kidney and the normal remaining kidney.

Certain findings are constant in these six cases and certain others are variable. The group is too small to allow more than the listing of findings. Obstruction to outflow in the diseased kidney is present in all six cases. All the surgical specimens show vascular changes similar to the usual findings in both kidneys in hypertension cases. All show aplastic lesions of the cortex with atrophy of the renal substance, scarring of the surface of the kidney, and decrease in renal substance. All show either active infection involving the cortical portion of the kidney or evidence of pronounced pyelonephritic changes of the healing changed condition. In two cases definite abscess formation in the renal substance is found. In all cases the hypertension seems to have developed comparatively rapidly, somewhere near a year, if one may judge by symptomatology and the duration of the apparent inciting cause. This is in contrast to the usual course of development of hypertension.

These cases vary from each other in their bacteriology. In Case 1 there was little pus, and, while culture was not reported, no bacteria were mentioned in the reports of the urine examinations. Pyelonephritis was noted both in the surgical specimen and in the remaining kidney at autopsy. Pyelonephritis of the kidneys, without infection being demonstrated, is frequently found at autopsy in hypertension cases with a definite history of remote inflammation with demonstration of the presence of an infecting agent. In two cases the colon bacillus was shown at the time of the hypertension, in one, staphylococcus only, and in two, mixed coccal and bacillary infections were present.

In four cases there is neither history of infection of the remaining kidney or of other organs, such as septic sore throat, nor of scarlet fever, which might produce hypertension. In two cases such other possible etiology is present; one has a history of scarlet fever and the other toxemia of pregnancy and bacteriuria in the remaining kidney, which is now bacteria-free.

After analysis of these cases and the demonstration of the findings common to all, one wonders why the condition does not develop more frequently, or not at all. In many surgical cases,

particularly in infected bilateral renal calculus cases, findings almost identical to these here described are noted with absence of hypertension the rule. Hypertension, as a terminal condition in such cases, is more common.

A brief survey of certain pertinent observations gleaned from physiologic and experimental medicine sources is presented for purposes of comparison with the above findings. Tigerstedt and Bergman,[17] confirmed by Hessel and Maier-Hüser,[8] have demonstrated an inner secretion of the kidney, derived from the cortex rather then the medulla, which they called renin. They determined that it is an internal secretion which is formed in the kidney, is given to the blood as it flows through the kidney, and acts through the peripheral vessel nerve centers, which in turn influence the tonus of the musculature of the peripheral vessels.

Hessel and Maier-Hüser contributed further by demonstrating that kidney extract executes a strong persistent elevating action on blood pressure. These authors link this action with that of secretions from the adrenal gland and also the hypophysis. Goldblatt, from his excellent study of hypertension, concludes that the cause of vascular hypertension is primarily a humoral one of renal origin. The cortex of the adrenal probably plays a part in the development of hypertension in addition to the "hypothetical" renal substance. Houssay and Fasciola,[9] repeating the work of Goldblatt and of Lynch and Sommerville, conclude that their experiments prove that the ischemic kidney secretes substances that cause permanent arterial hypertension. Volhard[19] states that excretion of indigo-carmine by one healthy kidney may be severely impaired by some reflex action or toxic substance from the diseased opposite kidney and may be found normal after surgical removal of the diseased organ. Volhard questions whether one can produce an increase in blood pressure of any considerable duration without the participation of adrenalin. He further states that adrenalin is secreted under physiologic conditions and plays a rôle in the maintenance of vascular tone and that clinical and experimental facts point to the kidney as the principal, and probably the only, source of the substance which instigates vascular hypertension.

Certain measures when applied to the kidneys of experimental animals fail to produce hypertension, and others produce it with regularity. I quote in part from Goldblatt's summary.

1. Bilateral nephrectomy produces uremia but no elevation of arterial pressure.

2. Extensive reduction in the amount of renal tissue by unilateral nephrectomy and damaging a portion of the remainder by ligation of a portion of the arterial supply or by coagulation necrosis produces a moderate degree of temporary elevation of arterial pressure.

3. Disturbance of renal substance by radiation by x-ray produces a moderate elevation of arterial pressure.

4. Infarction of portions of kidneys by multiple emboli does not produce hypertension.

5. Permanent obstruction of the ureter produces a moderate elevation of blood pressure.

6. Nephrotoxic substances (oxalate and uranium salts, et cetera) are of doubtful effect.

7. His own work, in which he produces ischemic areas in the kidney by clamping the arterial supply, producing partial occlusion of the vessel, results in hypertension. By variation of the condition of the experiments he proves his point forcefully that hypertension can be produced by this experiment and cured by elimination of the condition even after the lapse of months during which the hypertension has existed.

Volhard[19] recognizes some degree of hypertension (1) in every kind of anuria; (2) in urinary retention; (3) in polycystic kidney; (4) in pyelonephritic and hydronephrotic granular kidneys (hypertension is not infrequently found here); and (5) in hypoplastic kidneys. He elaborates occasional demonstration of granular kidneys and hypertension in amyloid disease, tuberculosis, and secondarily contracted kidneys from endarteritis due to syphilis. Albarran[1] recognized toxic nephritis in the normal kidney where its fellow showed a certain type of pathologic change in occasional cases. Volhard also notes that the lead kidney shows vaso-constriction which has nothing to do with the kidney tissue but produces suitable conditions for the development of renal disease. He ascribes a toxic condition which occurs in pregnancy to a substance of extrarenal origin which causes excessive vascular spasm, resulting in some cases in typical endarteritic changes in the vessels of the kidney with the end-result hypertension.

Clinically the following observations have been recorded. Fishberg[6] maintains that hypertension may occur in children in the presence of obstruction when there is extensive destruction of renal parenchyma. Volhard[18] and Schwarz[16] report hypertension in patients with contracted kidneys. Butler[4] says, "In spite of the frequency with which pyelonephritis is encountered in childhood, we have found no report of a serious hypertension occurring in the pyelonephritis of childhood before renal insufficiency was present." Longcope[11] states that the essential characteristics of hypertension associated with pyelonephritis consist in its bilateral occurrence usually with demonstrable or evident occurrence of obstruction to outflow of urine. Yet he records nine fatal cases of patients whose findings conformed to the above requirements without the existence of hypertension at the time of death. Weiss, Parker, and Robb[20] suggest that infection in pyelonephritis may heal, but that the hypertension initiated by it may continue to progress.

The present concept of the pathologic change in hypertension is that of endarteritic changes which tend towards partial occlusion of the arterioles of the kidney. This condition is approximated by Goldblatt's experiments. These arterioles are capable of spasmodic closure.

Moritz[12] (quoted by Butler in a personal communication) records three patients with essential hypertension and renal arteriolar sclerosis in which the lesion was limited to one kidney.

CONCLUSIONS

1. There is a small group of cases both in children and adults in which hypertension associated with unilateral renal disease either retrogressed as far as the patient has been followed or has been greatly, although temporarily, benefited by nephrectomy.

2. The constant findings in these cases are obstruction to the outflow of urine and damage to the renal parenchyma, which is in all cases extensive, hypoplastic in type, with involvement of the substance of the cortex of the kidney either in healing processes from infection or in still active processes with abscesses.

3. In five of the six cases reported, bacteria were still present in the infected kidney. No single type of infecting agent was encountered. Both coccal and bacillary types of infection were found.

4. Final end-result is now available in one case. Decreased hypertension recurred in a patient known to be nephritic previous to operation. Sufficient time has elapsed in another case in which toxemia of pregnancy was encountered, to indicate final results. Nephrectomy was followed by good health and freedom from hypertension for ten years. Hypertension is present in the eleventh year.

5. Striking recessions in blood pressure followed nephrectomy in all six cases. The lapse of time is not sufficient in four cases to allow of speculation as to outcome. The fall of blood pressure has persisted for two months in two, fifteen months in another, and twenty months in the fourth. In one of the two-month cases non-protein nitrogen was elevated in addition to the rise in blood pressure and fluctuated with it. While both the pressure and chemistry are normal, the excretion of phenolsulphonephthalein is not normal in the remaining kidney.

6. There are experimental and clinical data which indicate that such behavior of hypertension cases as is here indicated is theoretically possible.

7. Insufficient data exist at this time to allow of any attempt to explain the mechanism of the occurrence of improvement.

8. "Cure" is not necessarily the proper term to apply to these cases. Whether in the end cure is accomplished in any of the cases, nephrectomy appears to be a good therapeutic measure for prolongation of life.

* * *

I wish to acknowledge my indebtedness to Dr. J. Dellinger Barney for permission to quote his case from Butler, and to acknowledge additional data which he kindly supplied previous to his own report of the case.

I am also indebted to Dr. William C. Quinby, who kindly provided me with pathologic information which was not included in his original publication, and for end-results on his patient.

BIBLIOGRAPHY

1. Albarran, J.: Rein des Urinaires, Paris Thesis, 1889.
2. Barker, W. W., and Walters, W.: Hypertension associated with unilateral chronic aplastic pyelonephritis: Treatment by nephrectomy. Proc. Staff Meetings Mayo Clinic, 13:118, 1938.
3. Barney, J. Dellinger: Reported by Butler.[4] Other data supplied personally by Dr. Barney. For this favor credit is extended to him.
4. Butler, Allen M.: Chronic pyelonephritis and arterial hypertension. Jour. Clin. Invest., 16:889, 1937.

5. CRABTREE, E. GRANVILLE: Stricture formation in the ureter following pyelonephritis of pregnancy. Jour. Urol., 18:575, 1927.
6. FISHBERG, A. M.: Hypertension and Nephritis, 3rd Edition. Philadelphia: Lea and Febiger, 1934.
7. GOLDBLATT, H.: V. The pathogenesis of experimental hypertension due to eschemia. Ann. Int. Med., 2 (Old series xvi): 69, 1937.
8. HESSEL, G., and MAIER-HÜSER, H.: Verhandl. der Deutsch. Gesel. für Inn. Med., 46:347, 1934.
9. HOUSSAY, B. A., and FASCIOLA, J. C.: Buenos Aires. Extracted in Jour. A.M.A., 109:2002, 1937.
10. KINNELSTEIL, P., and WILSON, C.: Inflammatory lesions in the glomeruli in pyelonephritis in relation to hypertension and renal insufficiency. Amer. Jour. Path., 12:99, 1936.
11. LONGCOPE, WARFIELD T.: Chronic bilateral pyelonephritis: Its origin and its association with hypertension. Ann. Int. Med., 2 (Old Series xvi): 149, 1937.
12. MORITZ, A. R.: Quoted by Butler[4] as a personal communication.
13. PETERS, J. P.: The nature of the toxemias of pregnancy. Jour. A.M.A., 110:329, 1938.
14. PETERS, J. P., LAVIETES, P. H., and ZIMMERMAN, H. M.: Pyelitis in toxemias of pregnancy. Amer. Jour. Obst. and Gynec., 32:911, 1936.
15. QUINBY, WILLIAM C.: A case of marked hypertension in a boy of fourteen with congenital hydronephrosis and nephritis: Boston Med. and Surg. Jour., 189:485, 1923.
16. SCHWARZ, H.: Kidney diseases in infants and children. Amer. Jour. Dis. Child., 27:233, 1924.
17. TIGERSTEDT, R., and BERGMAN, R. G.: Kidney and circulation. Skandin. Arch. für Physiol, 8:223, 1898.
18. VOLHARD, F.: Die Doppelseitigen Hämatogenen Nierenkrankheiten. Berlin: Julius Springer, 1918.
19. VOLHARD, F., in BERGLUND, et al: The Kidney in Health and Disease, Philadelphia: Lea and Febiger, 1935; p. 245.
20. WEISS, SOMA; PARKER, F., JR., and ROBB, G. P.: A correlation of the hemodynamics, function, and histologic structure of the kidney in malignant arterial hypertension with malignant nephrosclerosis. Ann. Int. Med., 6:1599, 1933.
21. ZIMMERMAN, H. M., and PETERS, J. P.: Pathology of pregnancy toxemias. Jour. Clin. Invest., 16:397, 1937.

RENAL FUSION: UROGRAPHIC DATA AND THEIR CLINICAL SIGNIFICANCE

WILLIAM F. BRAASCH, M.D., and HOWARD J. HAMMER, M.D.

From the Section on Urology, The Mayo Clinic and The Mayo Foundation, Rochester, Minnesota

As a result of the widespread use of excretory urography, the presence of renal fusion has been recognized more frequently in recent years than in the past and the anomaly has become a rather frequent clinical problem. Operation for the relief of pain and the secondary complications which frequently accompany renal fusion is now being employed more often than formerly.

A review of the clinical records at The Mayo Clinic shows that 102 cases of renal fusion were observed during the past eight years (March, 1930 to 1938). Of this number, thirty-two patients were subjected to operation and one case was accidentally discovered in the course of the performance of abdominal exploration for other lesions. A review of the clinical and urographic data regarding these cases revealed many points of clinical interest.

In the first place, we were impressed by the need for a more accurate and a simpler terminology than that in current usage. Owing to the fact that renal fusion may assume a great variety of forms and may be variously situated, it has been designated by many terms. The term "horseshoe kidney" has been applied to the most frequently observed type of renal fusion because of its fancied resemblance to a horseshoe. When two kidneys are closely fused so as to form a rounded mass, the condition has been called a "lump" or a "caked" kidney. Occasionally the fused kidney assumes a sinuous form and it is then called an "S-shaped" kidney. When the fused kidney is situated in one side of the abdomen, the ureter leading to its caudad portion crosses the spine in the course of embryonic renal ascent and the anomaly is often referred to as "crossed renal ectopia."

These terms frequently are applied to different conditions by different observers and have no exact clinical significance. In order to simplify its terminology it would seem best to classify

renal fusion with reference to its vertebral relationship. Accordingly, it would be referred to as bilateral, prevertebral and unilateral. Renal fusion is bilateral when the two renal pelves are situated on opposite sides of the vertebral column. It is prevertebral when one or both pelves are situated anterior to the midvertebral line and unilateral when both pelves are situated on the same side.

Bilateral renal fusion frequently referred to as horseshoe kidney, occurs far more frequently than any other form and was encountered in eighty-four of the 102 cases reviewed. Prevertebral fusion was noted in five cases and unilateral fusion in thirteen cases. Most of the ensuing observations are referable to bilateral and prevertebral fusion. The data associated with unilateral fusion will be considered separately.

ROENTGENOGRAPHIC DATA

Data derived from careful inspection of the original roentgenogram may be of great clinical value and will often permit the recognition of renal fusion. The following roentgenographic data should call attention to the possible existence of this anomaly: (1) one or both renal outlines situated close to or partially overlapping the vertebral column; (2) the shadows of the lower poles nearer the vertebral column than those of the upper poles (normally, the reverse is true); (3) the lower borders of the two renal outlines continous and extending medially over the vertebrae; (4) an indefinite outline of a rounded mass overlying the vertebral column and (5) the renal outline at an unusually low level and associated with any of the other signs just enumerated.

One or more of these features were noted and proved to be sufficient to diagnose renal fusion in thirty-six (40 per cent) of the cases. The renal outline may vary in intensity in different films. If for some reason it is obscure, it is usually advisable to repeat the roentgenographic examination after the patient has had more thorough preparation. Because the renal outline is often accentuated in the excretory urogram, a suspicion of the presence of renal fusion frequently becomes a certainty when the excretory urogram is examined. This is particularly true in the presence of pelvic retention.

Careful inspection of the roentgenogram in cases of renal fusion often will reveal other data of clinical significance. Vertebral anomalies, such as spina bifida occulta and scoliosis, are observed more frequently in such cases than is otherwise usual. That scoliosis is observed more often in association with unilateral renal fusion is shown by the fact that it occurred in eight of thirteen cases of unilateral fusion. It might be expected that the outline of the psoas muscle would be obscured by the fused kidney. It is surprising, however, to note that the fused renal outline in no way interferes with the shadow of the psoas muscle which can be seen clearly in its entire extent.

Among other data which would suggest the presence of renal fusion on inspection of the roentgenogram should be mentioned arrangement, position and shape of the roentgenographic shadows caused by the presence of renal calculi. Such data were observed in eleven cases of bilateral renal fusion. In seven of these cases the stones were bilateral; in four, unilateral. These stones are necessarily either multiple or single; if single, they are large and coralliform. Multiple stones associated with renal fusion are found more frequently in the lower calices and because these calices usually extend toward the uniting isthmus, the included stones will be seen medially in the lower portion of the renal outline and isthmus. If one or more of the shadows caused by stones overlie the vertebral column, their shadow can be obscured easily by the vertebral shadow. When the stone is large and when it partially fills the renal pelvis, the cast of the stone will usually have a deformity similar to that of the shadow observed in a urogram.

Urographic Data.—A review of the urographic findings associated with bilateral renal fusion reveals anatomic data which may be of clinical value. Although the level of the renal pelves in relation to the vertebræ is variable, it is evident from Table I that their level is definitely lower than normal. These relationships were determined by a horizontal plane passing through the middle of the renal pelvis and the corresponding level of the spinal column. It is surprising to note how many times the renal pelvis was situated at the level of the fourth and fifth lumbar vertebræ. Although comparatively little difference

was noted in the relative level of the two pelves in most cases, the right segment and its pelvis were definitely higher than the left in eighteen cases and the left segment was higher than the right in fourteen cases. Because the outline of the right kidney is situated slightly lower than that of the left among normal individuals, when it is found to be higher, it may be regarded as additional evidence of the presence of fusion. In the prevertebral group, the pelvis overlying the spine is always on a lower level than the other pelvis.

The relative proximity of the two renal pelves to the vertebral margin is also of anatomic interest. It will be noted that the shadow of the right renal pelvis is more often situated closer to the midline than that of the left. This was definitely observed in twenty-six cases; in eleven, the shadow of the left renal pelvis was nearer the midline. Whereas the outline of the renal pelvis may be discrete, in many cases the shadow of one or more calices, usually the lower one, will overlap that of the vertebral margin. In other instances the shadow of the inner border of the pelvis is seen touching that of the vertebral border or overlapping it.

Although in such cases the distance separating the two pelves is usually less than that between normal kidneys, yet it may vary considerably. In fact, the two pelves are sometimes observed situated so far apart that renal fusion would hardly seem possible. The widest separation of the two renal pelves encountered in cases of bilateral renal fusion was 16.7 cm., measured from the mesial border of one renal pelvis at a point in its midportion to a like point on the medial border of the opposite side. Although the two pelves in cases of bilateral fusion are seldom so closely situated or interrelated as to contraindicate separation of the renal segments, in two cases the lower calices were so closely related that it became a factor of surgical importance.

Whereas the position of the pelves in cases of renal fusion is generally regarded as being fixed and rendered immovable by adherence to surrounding structures, ptosis of one or both segments can occur and may be urographically demonstrable. We have observed several cases in which the excursion of one segment on placing the patient in the upright position was described as greater than normal.

UROGRAPHIC INTERPRETATION

As has been previously stated, the recognition of renal fusion has been greatly facilitated in recent years by the routine use of excretory urography. The excretory urogram was employed in all of the cases in this series and it permitted clinical recognition in all but four instances (95.5 per cent). Failure in the four cases was explained by deficient visualization as a result of faulty preparation, reduced renal function and, in one instance, technical difficulties. The deformities suggestive of renal fusion are so apparent that more exact visualization by retrograde urography usually is unnecessary. Difficulty may arise, however, in distinguishing between renal fusion and the following conditions: (1) congenital single kidney with double pelves

TABLE I. RELATIONSHIPS OF RENAL PELVES TO VERTEBRÆ

Opposite Lumbar Vertebræ	Renal Pelvis	
	Right cases	Left cases
I to II	4	6
II to III	20	17
III to IV	25	22
IV to V	28	33
V and below	2	2

on one side and renal agenesia on the other; (2) bilateral incomplete rotation and (3) normal kidney on one side and renal ectopia on the same or the opposite side.

The first condition mentioned which may resemble unilateral fusion, usually can be recognized by the fact that the two ureters are seen extending down the same side to the bladder or uniting with one another at a variable distance below the renal pelvis. In cases of unilateral fusion, on the other hand, the ureter leading to the lower renal pelvis can be seen crossing the sacral vertebræ to the opposite side of the bladder. This condition has often been called crossed renal dystopia.

Incomplete rotation of one or both kidneys is frequently observed without the presence of renal fusion. Although as a rule, the anatomic level of the incompletely rotated kidney is slightly

lower than the normal, nevertheless it may be observed in the normal position. If both pelves are incompletely rotated, the condition may be easily confused with renal fusion. Although the distance separating a normal kidney from an ectopic kidney usually is so great that fusion would be improbable, nevertheless we have learned from experience that wide separation does not necessarily exclude the possibility that fusion is present. Normal excursion of the pelvic outline in one or both kidneys, would usually exclude the presence of fusion but not always. The possibility of prevertebral fusion being present must be excluded in all of these cases. Urographic recognition may be difficult in cases of prevertebral fusion when the lower renal pelvis is either obscured by the vertebral outline or the function of that segment is insufficient to enable visualization of the pelvis.

Urographic Recognition of Renal Fusion.—The deformities of the pelvis characteristic of renal fusion have been described fully by several observers. The position of the calices, extending in a reversed direction from the normal, combined with direction of the axis of the lower calices toward the isthmus, are probably the most characteristic urographic data in the recognition of renal fusion. The latter characteristic was observed in all but seven cases and is the most important factor in distinguishing between fusion and incomplete rotation of otherwise normal kidneys. Abnormal axis of the calices was noted as bilateral in eighty-two (91 per cent) of the cases. Evidence of incomplete rotation in only one segment of the kidney was noted in six cases and in one case there was no evidence of abnormal rotation on either side. Abnormal rotation of the pelvis so that its axis is horizontal was characterized by a caudad direction of the calices and was noted in nine cases, all on the right side.

The unusual relationship of the ureter as it leaves the pelvis is also characteristic of renal fusion. Although visualization of the ureters is often fragmentary in the excretory urogram, nevertheless the relationship of the ureter to the pelvis was visualized in fifty-two of the cases. The pelvic insertion of the ureter was definitely lateral or anterolateral in fourteen cases. In fifteen cases the ureter was visualized on only one side and, of these, the insertion was anterolateral in nine and anterior in six.

UNILATERAL FUSION

The roentgenographic and urographic data associated with unilateral renal fusion are considered separately because they are different from those associated with bilateral fusion. Unilateral fusion occurred in thirteen of the group of 102 cases of fusion reviewed. The renal outline associated with unilateral fused kidneys often is not clear and usually does not have the diagnostic significance observed in cases of bilateral fusion. The outline of a large mass confined to one side of the abdomen, with absence of the renal outline on the other side, should suggest the presence of unilateral renal fusion. Because, in most of these cases, the renal outline is situated below the usual renal position, it may be confused with shadows caused by other intra-abdominal conditions. Apparent enlargement of the hepatic outline with hepatic ptosis is sometimes associated with unilateral renal fusion. Whether the absence of the kidney from its usual position is a factor in causing such ptosis is open to question. Failure of visualization of the shadow of the psoas muscle may be observed with unilateral fusion on the side of the crossed kidney, as has been observed in cases of renal agenesia.

The relation of the two pelves to one another in the urogram assumes much greater surgical importance with unilateral fusion, because the pelves were situated so closely together in five cases that separation of the two segments would have been difficult or impossible of accomplishment. In the other cases the distance separating the pelves was definite, the average distance being 2.8 cm. and the greatest 8.5 cm. In one case, renal rotation was such that both pelves were on the same level.

Distinction between unilateral fused kidney and a single kidney with duplicated pelvis is made possible by visualization of the ureter leading to the lower pelvis as it crosses the sacral vertebræ. This could be seen in the excretory urogram in eleven of the thirteen cases observed. In two cases opaque catheters would have made it more visible, as was recently noted by Beer and Ferber.

Evidence of stasis was found in nine cases of unilateral renal fusion. This occurred in the upper segments in five cases, in the lower in eight and in both segments in four. In four cases the degree of stasis was grade 3 or higher, and only grade 1 or 2 in the others on the basis of 1 to 4. A difference in the size of the pelves was noted in every case.

Multiple pelves were observed in four cases of unilateral fusion. In two cases, two pelves were visualized in both the upper and the lower segments of the kidney. The upper of the duplicated pelves may be exceedingly small and its outline may resemble a single detached calix.

COMPLICATIONS

Deformity of the outline of the calices or pelvis, or both, is noted frequently in cases of renal fusion (Table II). It is characterized

TABLE II. DEFORMITIES AND COMPLICATIONS ASSOCIATED WITH BILATERAL RENAL FUSION (EIGHTY-NINE CASES)

Deformities or complications	Cases	Per Cent
Pyelectasis, caliectasis and ureterectasis	72	81
Pyelectasis:	51*	57
Right	19	21
Left	16	18
Bilateral	16	18
Caliectasis:	56**	63
Right	19	21
Left	20	22
Bilateral	17	19
Ureterectasis	7	8
Complications:		
Calculus	22	25
Pyelonephritis (cystitis 14; prostatitis 19)	6	7
Pyonephrosis	3	3
Tuberculosis	3	3
Tumor	2***	2

*Grade 3 or more; 14 cases (16%)
**Grade 3 or more; 14 cases (16%)
***Suspected in 2 cases; patients did not remain

by a moderate degree of apparent dilatation. It was confined to the calices in seventeen cases (19.1 per cent) and to the pelvis in sixteen (18 per cent). In some of the cases associated with evident pyelectasis, several of the calices appeared to be normal, whereas others were slightly dilated. However, in the majority of

cases, pyelectasis and caliectasis were coincident and occurred in seventy-two cases (81 per cent). Pyelectasis was noted on one side only in thirty-five cases, occurring on the right side in nineteen and on the left in seventeen. That stasis will occur more often in the lower lying pelvis in cases of renal fusion is demonstrated by evidence of pyelectasis found in twenty-nine of thirty-two of the pelves so described. In interpreting the urogram in cases of renal fusion it should be remembered that the pelvic outline associated with incomplete rotation differs from the normal. The outline of the calices which extend anteriorly if visualized head-on may give the impression of being dilated.

Pyelectasis, as a rule, is only of moderate degree and in some cases is very slight. In fourteen cases, however, pyelectasis was grade 3 or more (on a basis of 1 to 4). Pyelectasis of even slight degree may assume clinical importance when the patient's symptoms suggest the possible presence of renal stasis. Varying degrees of pyelectasis have been observed among patients who never complained of any pain, indicating that stasis is not necessarily an etiologic factor. In fact, pyelectasis of slight degree has been regarded by various observers[2] in some cases as a congenital abnormality rather than as a pathologic complication. Slight pyelectasis without evident obstruction also has been associated with fused kidneys and seen at necropsy.

It therefore becomes of considerable importance to determine whether the evidence of pyelectasis in the urogram is evidence of stasis. Unless the pyelectasis or caliectasis is of such a degree that it is easily recognized as abnormal, other steps should be taken to determine the existence of stasis. This can best be done by emp'oying a method of delayed retrograde urography which should be used more frequently in these cases than it has been heretofore. Retrograde urography, moreover, may reveal phases of deformity not revealed by the excretory urography. Because the employment of solutions of organic iodide has rendered bilateral retrograde urography comparatively innocuous, the use of delayed films in cases of renal fusion may well be justified. The presence of stasis is also suggested by the persistent or increased visualization of one or both pelves in the excretory urogram made sixty minutes and more after the injection of intravenous media. Intravenous urograms made in the erect and dorsal positions may also be of diag-

nostic value in determining the existence and relationship of postural excursion.

Pain caused by renal fusion is often of such an indefinite character and is so easily confused with lesions in the surrounding organs or tissues that its clinical identification may be extremely difficult (Table III). That such pain is not necessarily caused by stasis is

TABLE III. SUMMARY OF CHARACTERISTICS OF PAIN*

Sites of pain	Pain		Total cases
	With extension, cases	Without extension, cases	
Lumbar or costovertebral		23	42
Extension to groin or inguinal region	6		
Extension to lower part of abdomen	4		
Extension to flank or loin	4		
Extension to symphysis or bladder	3		
Extension to thigh	2		
Lumbosacral		10	12
Extension anteriorly	2		
Abdominal		3	18
Upper abdominal region	8		
Lower abdominal region	10		
Extension to costovertebral region	7		
Extension to inguinal region	5		
Extension to bladder and genitalia	3		

*Pain present in some form in seventy-two cases (70.6 per cent).

borne out by the fact that it may occur in the absence of any urographic evidence of stasis. That patients without evidence of renal stasis may be relieved of pain by nephrolysis or surgical separation of the two renal segments with nephropexy is indicated by the postoperative relief in several cases reported. However, the failure of relief following this operation in other cases which are not reported may make the procedure of questionable value unless there is evidence of the presence of stasis. To add to the confusion, cases are observed in which there is very evident pyelectasis on one side,

with a history of previous but not recent pain. Several of these patients remained symptomless over a period of many years prior to observation.

SUMMARY

The clinical recognition of renal fusion has become more frequent in recent years as a result of the routine use of excretory urography. Clinical recognition by this method was possible in 95.5 per cent of 102 cases reviewed. There is need for a simpler terminology. Adapting the vertebral column as an anatomic basis, renal fusion may be classified as bilateral, unilateral and prevertebral. This eliminates the necessity for using such indefinite terms as "horseshoe" kidney, "caked" kidney and "crossed renal dystopia."

Careful inspection of the renal outline in the original roentgenogram should permit recognition of bilateral fusion in about half of the cases. The recognition of unilateral fused kidney by its outline is less frequent. The arrangement of multiple shadows of stones and the characteristic outline of large single stones in cases of renal fusion will often indicate the presence of the anomaly.

The position of the renal pelves in cases of bilateral fusion is variable but the following features are of interest: (1) the low level of one or both renal pelves in relation to the vertebræ—more than 60 per cent being below the third lumbar vertebra—and (2) the closer proximity of the right pelvis to the vertebral margin than the left pelvis. Although the two pelves usually are situated closer together than normally, the distance separating them is not uniform and it may be so great that the presence of fusion would seem impossible. In one case, the distance separating the pelves was 16.7 cm. Approximation of the pelves with renal dystopia may simulate fusion. Although the pelves in cases of renal fusion are frequently fixed by surrounding tissues, considerable excursion may be visualized in one or both segments.

In differential diagnosis which may be difficult, the possibility of the presence of the following conditions should be eliminated: (1) bilateral renal fusion and incomplete renal rotation with ectopia and (2) unilateral renal fusion and crossed renal dystopia without fusion. Recognition of the presence of prevertebral fusion may be difficult when the lower pelvis is obscured by the vertebral shadow or when there is insufficient function in that segment. Probably

the most significant diagnostic factor in the recognition of fusion is the characteristic axis of the lower calix, which is usually directed toward the isthmus. The relation of the pelves to one another in the urogram in cases of unilateral fusion may be of surgical importance. In many cases, the two pelves are so closely interrelated that separation of the respective renal segments would be difficult or impossible.

Evidence of dilatation in either the calices or the pelves, or both, is associated with many cases of renal fusion. This usually indicates the presence of stasis, although in some cases it does not. Pyelectasis and caliectasis were sometimes observed among patients who never had pain. Lumbar pain is sometimes observed among patients who do not have evidence of pyelectasis or caliectasis. Fused kidneys removed at necropsy may show gross evidence of a minor degree of pyelectasis without apparent ureteral obstruction. In some cases, this may be a residual deformity caused by previous obstruction. In other cases, however, it may be inferred that pyelectasis is a congenital abnormality rather than a pathologic complication. The existence of renal stasis can best be demonstrated by the use of the delayed retrograde urography and renal stasis will be found present to a variable degree in many cases of renal fusion. It may be a variable factor in indicating the cause of obscure lumbar or abdominal pain.

REFERENCES

1. Beer, E., and Ferber, W. L. F.: Crossed renal ectopia (unilateral fused or elongated kidney) with report of fourteen cases (clinically diagnosed and two cases encountered at autopsy during the past eighteen years). Jour. Urol., 38:541-561, (Dec.) 1937.
2. Braasch, W. F.: Anomalous renal rotation and associated anomalies. Jour. Urol., 25:9-21, (Jan.) 1931.

DISCUSSION

PRESIDENT RANDALL: I wish, if I may, to take this opportunity to discuss the presentation which Dr. Crabtree has brought before you; in so far as no one has taken the floor promptly, I have a fear that you aren't cognizant of the importance of it. To me Dr. Crabtree's presentation is probably one of the most important papers that have been presented at this meeting.

I want to draw your attention to the fact that I am convinced there is a large chapter of urologic surgery that is just beginning to be opened to us, and Dr. Crabtree's presentation of it is the first that has appeared on any of our programs; that is, the relationship between surgical renal pathologic lesions and hypertension. There is a vast amount of work being done in the medical departments of the country on hypertension. They are stymied by that horrible term "essential" hypertension, which means here, as elsewhere, that we don't know why the hypertension exists.

We have all been interested, of course, in the remarkable work of Goldblatt in trying to show that hypertension can be experimentally produced by creating a renal ischemia, not only renal ischemia, but *unilateral* renal ischemia.

In the early part of last fall certain ideas were crystallized in my mind and I went to our medical department with a theorem. We are very fortunate in having on our medical staff Dr. Eugene Landis, who has been doing some very interesting, thorough and most painstaking work in nephritic cases in the hospital.

I approached him with a group of correlated ideas; first of all, by telling him that the urologists are the only people who have cured hypertension (which we have known for twenty-five years in the picture of hypertension that is associated with prostatism); secondly, the idea of Goldblatt's conclusion that a renal ischemia is at the base of these cases of so-called renal hypertension—a number of which are the so-called "essential" hypertensives; thirdly, the idea of the work of one of our members, Dr. Hinman, who when studying an entirely different, though now related, subject, that of hydronephrosis, showed that the renal atrophy that goes with experimental hydronephrosis is not the atrophy of pres-

sure alone, but he himself fifteen years ago called it "ischemic atrophy."

I said to Landis, "If that is experimentally recognized—and I am sure it is—if Goldblatt's story is one of renal ischemia, then there must be something closely associated between obstructive uropathics and hypertension, and therefore there should be urologic evidence of the same."

Starting this last fall, with splendid and interested coöperation, we asked that, in those cases where they had nothing else to put their finger on to explain a hypertension, they call for a urologic consultation.

Therefore, during the course of this last winter, we have experienced exactly what Dr. Crabtree has reported. We have been picking up individual cases here and there of renal pathologic lesions. Our most striking ones are two in which there was a long standing obstruction and infection, and the most interesting thing about it all is—it bears out Dr. Goldblatt's experimental work—that it can be a unilateral condition. In nephrectomizing such patients we have seen exactly the same remarkable results with alleviation of the hypertensive state.

I am certain that our program for the next few years is going to be replete with reports of this most interesting observation. I am sure that if you get the coöperation of your medical departments you are going to find an entirely new field for surgery and, what is more, it will be surgery in otherwise incurable cases.

Dr. Archie L. Dean (New York, N. Y.): It is my impression, in the early stages of a study as interesting and as important as Dr. Crabtree presented, that we should get all of the information available from different angles and later, when we know more, try to interpret our findings.

I would like to mention a lesion which Dr. Crabtree didn't present, namely, papillary tumors of the renal pelvis and ureter. These in the unilateral cases unquestionably have obstruction, infection, and destruction of the renal parenchyma, all to a marked degree. In a small group of cases (approximately ten) which I have been able to follow, some for as long as ten years after operation, the hypertension which existed in practically all of the cases before operation has not been reduced.

DR. J. DELLINGER BARNEY (Boston, Mass.): I think the Association is to be congratulated upon the able way in which Dr. Crabtree has presented a most striking lesion, about which we know relatively little. He mentioned a case of mine, and I shall eventually report that *in extenso* together with certain other cases.

I might say that this child had been seen for some time before the kidney was taken out, or before it was realized what we were dealing with, and she did have one of those atrophic kidneys, about one-quarter the size of a normal kidney. What enlargement existed was at the expense of the pelvis, there being very little, if any, cortical tissue left. There was no particular obstruction. I can't say what the cause of dilatation was unless it was infection, but the pathologist noted in the sections the extensive changes in the blood vessels, for example, the sclerosis of the arterioles, and so on.

The results postoperative were most dramatic, in that she had a blood pressure of 192 over 110 observed on various occasions for a long time before operation occurred, and almost immediately, a day or two after operation, her blood pressure fell to 110/60, or something like that. She has been seen and observed on numerous occasions since; her blood pressure is now 92/60, and she is perfectly well, without headaches, and so on, that she had before.

As a result of this, of course, all of us, urologists and medical men, are now scrutinizing every case that we see with any renal infection at all, taking blood pressures all the time, seeing if we can't hook up hypertension and renal infection. We have several cases under recent or under present observation which seem to bear upon the subject, but it is surprising how many, which seem to be the cases we are after in some way or other, do not quite fit in. But we are going to find as time goes on (and I am talking like this trying to arouse a universal interest) that we have overlooked many of these cases which have existed right under our noses and we are going to find more, so that eventually we shall have quite a large collection of cases and we shall know a lot about it. It is a very interesting subject.

DR. WILLIAM F. BRAASCH (Rochester, Minn.): The patient reported by Walters and Barker, referred to by Dr. Crabtree in his paper, suffered from a chronic unilateral atrophic pyelone-

phritis. Some forty patients with this lesion have been observed at the Mayo Clinic. This is the first and only case of this type I have observed in which hypertension was relieved by nephrectomy. Although several of these patients had hypertension, this is the only case which I can recall in which the hypertension dropped following nephrectomy.

Several years ago I thought that hypertension in a patient with coincident hydronephrosis might be benefited by removing the affected kidney. This was done in some three or four cases, but no drop in the hypertension followed removal of the hydronephrotic kidney. Similar observations were also made in a group of cases of renal stone with hypertension. Removal of the stones and the infection in these cases caused no difference in the blood pressure.

Although I am not much of a clairvoyant, I doubt very much that many patients of the type described by Dr. Crabtree will be relieved by nephrectomy. I am inclined to predict that many more patients will be operated on futilely and without any resulting decrease of the hypertension. Reduction in hypertension will follow in only a very small group of cases which possess specific conditions which we yet have not discovered. However, it opens up a very interesting field for future investigation.

DR. JOHN B. WEAR (Madison, Wis.): The interesting point about these kidneys is that grossly there may be the same changes in two different kidneys and one will cause high blood pressure and the other will not. It seems to me that some hormonal aspects of the kidney must be considered. This pressor substance which has been mentioned may be either hormonal in nature or it may be a product caused by certain lesions of the kidney. When we consider the well-known function of the kidney in making ammonia with urease, the idea of a pressor substance may be analogous.

PRESIDENT RANDALL: I think Dr. Braasch has the cart in front of the horse. It isn't that pyelonephritis is a factor that should produce hypertension; these patients will come to us because of hypertension, and that is the symptom on which we would consider the question of operation and not as to whether a pyelonephritis is coexistent.

I would like Dr. Crabtree to answer a question of the factor of obstruction in these cases and whether obstruction is again the basic thing with or without infection.

DR. E. G. CRABTREE (Boston, Mass.): I want to thank those men who have emphasized my point of view, that here is a field of usefulness for urology in hypertension cases if we would but take it up.

If you will think back carefully on my presentation of the paper, you will note that I offered no explanation for this phenomenon which occurs in some cases and does not occur in similar cases. I presented an extract from physiologic and medical literature as a *comparison* in findings and not an explanation of findings. I think there is an "x" factor, as Dr. Braasch has said, which determines why some of these people may have hypertension and some do not. In a two-bed ward the patient (Case 6) whose history I reported last was lying beside a man who had almost the identical infection problem, and bilateral obstructive lesions; one of his kidneys was atrophic, badly damaged in its cortical substance, the other hydronephrotic. His blood pressure had never risen, and has not changed after operation. In no way did he participate in the same hypertensive changes which the other man did. So there must be an "x" factor somewhere. I tried to bring out in the beginning of the paper that we all see cases of known infection and obstruction of twenty years duration or longer with no change in blood pressure. There is some other factor than the obvious ones.

I believe, since Dr. Barney's case is inadequately presented by Dr. Butler and me (who have the habit of presenting his cases before he presents them), that when he eventually publishes his report it may prove to be very much of an addition to the literature.

Dr. Dean's remark is a pertinent one, and yet I think his patients fall into this same group of cases in which apparently the same factors which I have described exist, except without the hypertension. We must give consideration to Dr. Randall's statement that our approach to these patients should be with our eyes open as to the presence of hypertension and a consideration of the possibility as to whether nephrectomy might cure them.

What I have said already probably answers Dr. Randall's question regarding obstruction. Certainly, all of these cases had evidence of hydronephrosis and two of the patients were non-catheterizable on the affected side. Obstruction was present in marked degree in every one of these cases. Whether it was the important factor or not I cannot say. Cortical destruction in these kidneys was also a universal finding.

I agree with those who have discussed this presentation that urologists can and should inform themselves sufficiently to allow them to participate along with medicine in recognition and treatment of this group of hypertension cases. The six cases presented are an inadequate group. No doubt other cases will be added rapidly now that the subject is opened up, and there may be other cases buried in the literature which I have been unable to find, which will now be brought out and made available for study.

DR. WILLIAM F. BRAASCH (Rochester, Minn.): In answer to Dr. Howard's question, I might say that when a patient tells me that the radiation of his pain extends to his shoulder, I invariably dismiss him from the field of urology. However, it is true that radiation of pain with renal fusion is often most outlandish and bizarre. Shoulder radiation of pain with renal fusion must be extremely rare.

EARLY PHASES OF PROSTATIC HYPERPLASIA

CLYDE L. DEMING, M.D., AND CHARLES NEUMANN, M.D.

From the Departments of Surgery and Pathology, New Haven Hospital, and Yale University, New Haven, Connecticut

Many theories have been proposed by men interested in the various branches of medicine to explain the development of benign prostatic enlargement in man. An extensive study of the gross and microscopic lesions has been made, but insufficient attention has been given to the early phases of the enlargement. The urologist frequently observes that the benign enlargement of the prostatic gland which he sees at operation is covered by a thin layer of posterior urethral epithelium. In many instances, the tumor seems to replace most of the prostatic gland. There is full agreement with regard to the histologic constituents of the surgical specimens. They are composed of glandular, fibrous, and muscular tissues, but the relative amounts of these tissues are variable. The fact that there is a preponderance of the glandular tissue has led investigators to presuppose that the enlargements are mainly glandular in origin. The wide distribution of the glandular nodules in the various lobes of the prostate is further evidence in support of this theory. One of the outstanding declamations is that of Marion and Zuckerkandl, who believed that these enlargements begin in the glands of Albarran. Velpeau, as early as 1841, recognized fibromuscular masses. Thompson, in 1873, was inclined to believe that the primary tumors bear some resemblance to early uterine myomata. As late as 1929, Kausch, in Germany, suggested that the glandular elements are derived from the deep urethral glands. Keyes, Hinman, and Randall adduce evidence from the material studied to show that most of the foregoing theories of early development of "prostatic hypertrophy" are justifiable.

It is necessary to have more definite knowledge concerning the early anatomic phases of benign prostatic enlargement before its cause can be logically established. It is the object of this paper to attempt to throw more light on the first and foremost part of the problem, namely, the beginnings of the so-called prostatic hypertrophy. In the prostatic glands which we see at the operating

table, so much disorientation of the components of the organ has been produced by growth, pressure and atrophy that little information is to be obtained from a study of them. The basis for consideration of the early anatomic lesions of the so-called prostatic hypertrophy is the study of anatomic specimens of prostates ob-

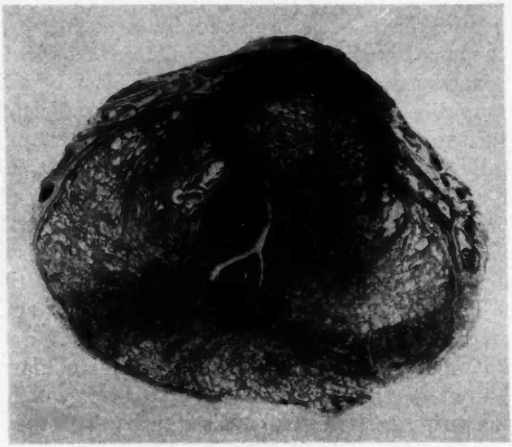


Fig. 1. Photomicrograph (2×). Prostate of man seventy-two years old. Section near veru, showing fibromuscular nodule near urethra.

tained at autopsy from subjects forty-five years of age and upward. From the microscopic study of minute, early lesions one can hope to show where and how the lesion originates.

The specimens were fixed in 10 per cent formalin solution and cut transversely at five different levels. When small nodules were discovered, either with the naked eye or by microscopic study, serial sections were cut of the entire transverse section involved, and the nodule or nodules were followed up and down the prostate to their terminations. Various stains were used, but the hematoxylin-eosin and Masson trichrome stains have proved the most satisfactory, the latter being employed to differentiate muscle from fibrous tissue. The large and complete sections were first studied by throwing the entire section on the screen with the projectoscope. This gave an opportunity for comprehensive study of the architecture of the gland as a whole which it is impossible to obtain by

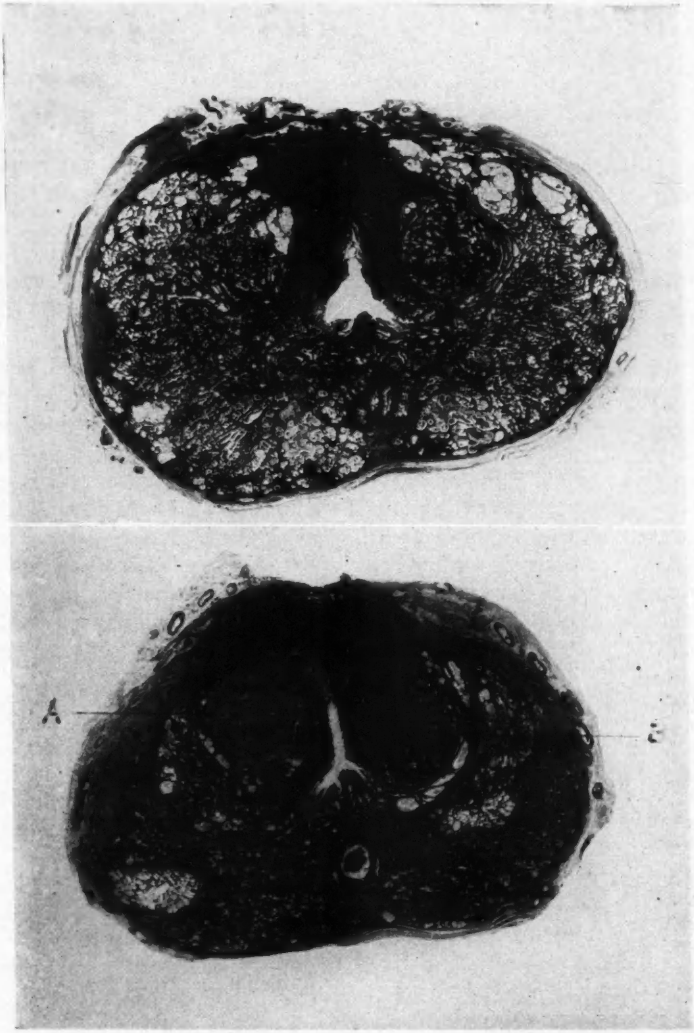


Fig. 2. *(above)* Photomicrograph (2×). Prostate of man sixty-eight years old, showing glandular nodule in lateral portion of muscular urethral wall. Glandular nodule contains heavy muscular stroma.

Fig. 3. *(below)* Photomicrograph (2×). Prostate of man seventy-four years old, showing bilateral tumors, (*A*) a fibromuscular nodule half invaded by glands and (*B*) a small glandular nodule on opposite side.

the use of the microscope. For minute, localized detail of the sections, the microscope played its part.

From 150 specimens, twenty-four prostates with sufficiently early lesions have been studied. The specimens contain aglandular and glandular areas in various stages of development. In most of the specimens the two lesions exist together. In six of the prostates, only aglandular masses are found. In none of the specimens do glandular nodules exist without aglandular areas.

The aglandular areas are found within the musculature of the urethral wall. They may be single (Fig. 1) but are more often multiple and bilateral, located anywhere within the musculature of the urethral wall between the external and internal sphincters. As they develop in size, they tend to become round and oblong in shape and may later become quite large and encapsulated. As the result of localized outgrowths or of the union of two or more of the developing centers, they may assume a nodular appearance. That these aglandular nodules develop to a size sufficient to cause urinary obstruction has been well demonstrated by Hinman and Sullivan, Mitchell and Blaisdell, and Veseen. In the routine histologic examination of surgical prostatic specimens, it is not uncommon to find masses of solid tissue and even definite, encapsulated, aglandular nodules in the presence of glandular nodules. Patch and Rhea found that 25.4 per cent of 181 consecutive surgical specimens of so-called prostatic hypertrophy showed leiomyomatous nodules varying in size from 0.5 to 3.0 mm.

The glandular nodules vary in size and are surrounded by circular muscle fibers (Fig. 2). The acini within a nodule may show active budding projections and dilated cystic areas. Cystic dilatations may appear early, but corpora amylacea are not seen in the early lesions. The glandular nodules are found in the muscular wall of the urethra (Fig. 3) and have not been seen in the lateral and posterior lobes. When these nodules increase in size, they deflect the urethra greatly, compress the true lateral and posterior lobes, and appear as lateral lobes on either side of the urethra. They apparently do not develop from the suburethral glands of Albarran, as was formerly thought.

The study of serial sections has led the authors to believe that the glandular nodules are a result of the invasion of an aglandular nodule by epithelial buds from an adjacent duct. These epithelial

buds may enter the solid nodule laterally or centripetally and form glands. Because the glands grow more rapidly than the muscle and collagenous tissue, they may entirely replace the muscle tissue and cause the nodule to appear wholly glandular. As the peripheral muscle tissue becomes compressed, it forms the "surgical capsule" of the glandular mass. This method of glandular tissue formation from ducts is similar to that seen in the normal embryologic budding from the posterior urethra, which forms the anlage of the prostatic glands. This process may be a re-awakening of the activity possessed by these ducts during the embryologic period. One can readily demonstrate this epithelial response on the inside of a duct adjacent to an aglandular nodule, while directly across its lumen the epithelium is dormant (Figs. 4 and 5).

In this study, glandular nodules have not been found in the lateral and posterior lobes of the prostate. Aglandular nodules have been seen in the roof of the urethra and below the crista urethralis, from which hyperplastic lobes could theoretically develop. The anterior and middle hyperplastic lobes have not been studied, nor have we found the reason for the occurrence of an isolated glandular lobule within the bladder at some distance from the prostate and not connected with it. A continuation of these studies should undoubtedly reveal these mysteries.

Since the glandular component of the prostatic hyperplasia is seen to be derived from the prostatic ducts within the urethral muscular wall, one would like to analyze further the origin of the aglandular nodules. The fibromuscular nodules of the prostate resemble histologically the fibromyomata of the uterus (Fig. 6). The uterine tumor has been shown to develop from a muscle cell. The sinus utricularis is the homologue of the uterus and hence of Müllerian duct origin. The work of Lowsley, Walker, and others on the embryology of the prostate and urethra discloses the fact that the muscle fibers of the lower Müllerian duct system meet the muscle fibers of the Wolffian duct system in the posterior urethra and intertwine themselves with the muscles which come down from the ureters, trigone, and bladder. The largest number of solid muscular nodules is found near the utricle and below its floor (Fig. 7). The aglandular, fibromuscular tumors develop around small blood vessels which increase in numbers with the growth and nourish it (Fig. 8). Whether the nodule remains

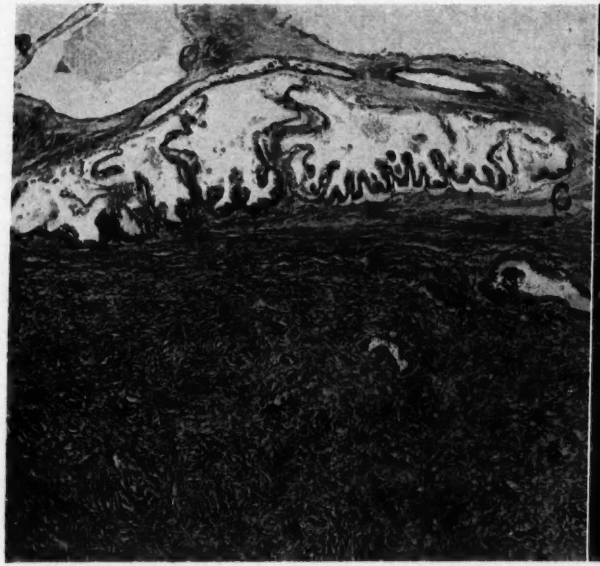


Fig. 4. Photomicrograph (50×). Prostate. Fibromuscular nodule with budding duct branches adjacent to the nodule but external to capsule (*C*). Note epithelial proliferation on duct wall adjacent to nodule and relative inactivity on its opposite wall.

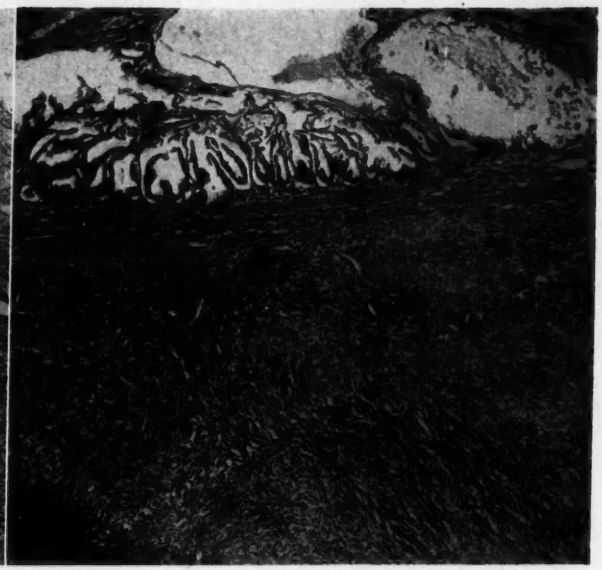


Fig. 5. Same as Figure 4, 100 microns distant.

fibromuscular or is transformed into a glandular nodule depends on whether or not the primary nodule is invaded by the epithelium of an adjacent duct.

Further evidence to support the hypothesis that these tumors of the prostate arise from the vestigial component of the Müllerian

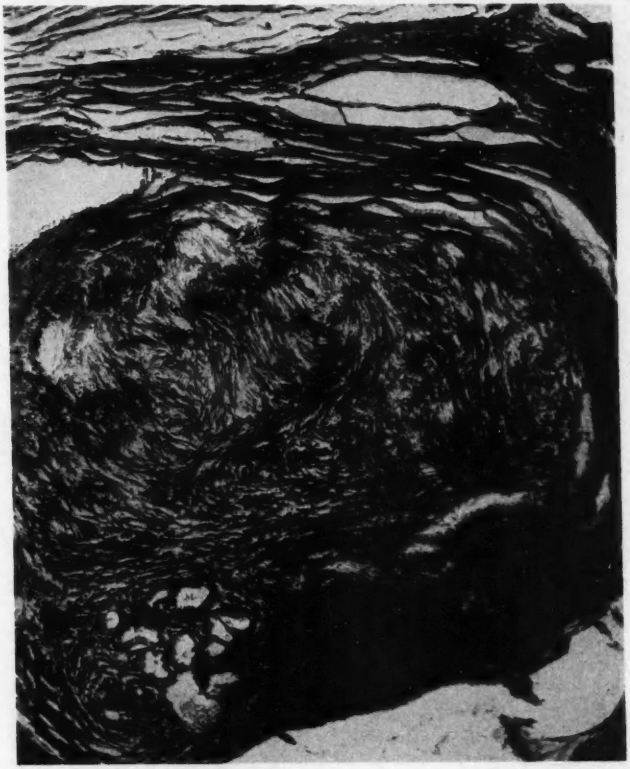


Fig. 6. Photomicrograph (50×). Prostate. Fibromyomatous nodule in man sixty-seven years old. Note capsule. Few glands in one side and definite whorl of muscle fibers resembling uterine myoma.

system may be elicited from a consideration of activity produced in homologous vestigial organs by hormones. In the dog, all the prostatic glands are derived from the epithelium of the utricle,

which is very sensitive to estrin (Zuckerman). In rodents and the rhesus monkey, part of the glands of the prostate take their origin from the urethral buds and part from the sinus epithelium, while in man all of the prostatic glands have been shown to originate from urethral epithelial buds. Further study along this line should add materially to the practical issues involved in tissue reactions to hormones.

Our present knowledge of these specific reactions, although limited, is supported by Lower and his co-workers, who have produced a physiologic hypertrophy of the prostate in dogs and rats. As far as the authors are aware, no one has ever demonstrated a

Fig. 7. Photomicrograph (2¾×). Prostate of man sixty-four years old. Note small light areas below floor of urethra representing early fibromuscular nodules. Three glandular nodules are also present.

pathologic benign prostatic enlargement in dog, rodent, monkey, or horse which caused retention of urine, nor has such a lesion been produced experimentally in animals. All of the experimentally produced prostatic enlargements are physiologic hypertrophies, not tumors or hyperplasias. We must not confuse them with the pathologic lesion in man. The natural prostatic enlargement in the old dog compares histologically with the experimental enlargement produced by testicular hormonal injections. It can be re-

duced by removal of the testicular hormone or by castration of the dog. Castration in man has failed to show any effect on the pathologic prostatic enlargement. The fact that benign pathologic enlargement of the prostate has been found in eunuchs leads one to minimize the part played by the testicle in its development.

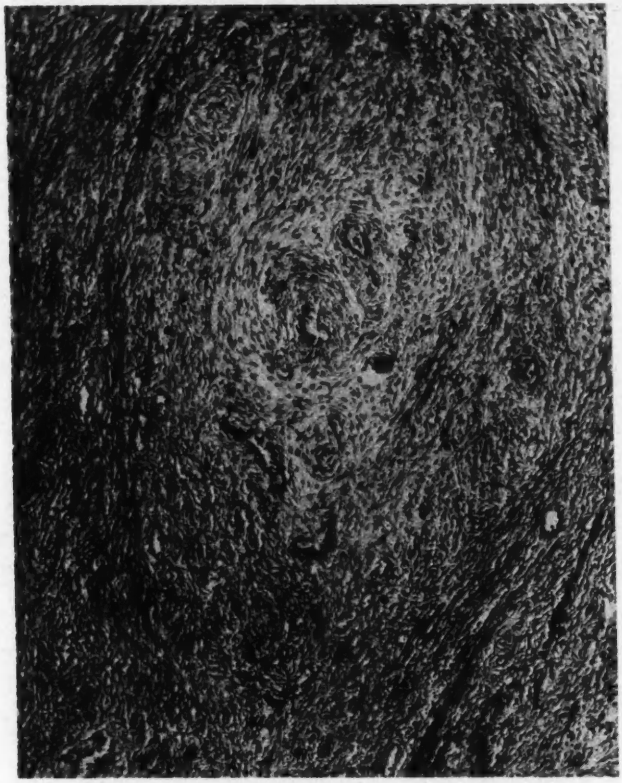


Fig. 8. Photomicrograph (50×). Prostate. Early fibromyomatous nodule forming around vessels.

Rothschild, Greene and Brooks believed prostatic enlargement to be the result of inflammation, as suggested by Ciechanowski; but Cabot and Smith have clearly demonstrated that men with histories of infection are less likely to develop a "prostatic hyper-

trophy." Prostatic enlargement is not due to arteriosclerotic changes, because it occurs in individuals who do not have arteriosclerosis. Reischauer's theory of compensatory hypertrophy is illogical. Kausch has correctly ruled out the adenomata theory, because the growth does not fulfill the criteria enunciated for adenomata. We have shown that the enlargement does not begin in glands, nor is it necessarily derived from glands. If it was derived from the musculature around a duct or gland, the primary nodule should show a duct or gland within its center. This has not been shown in our observations.

SUMMARY

This work definitely discloses that the early change of benign enlargement of the prostate in man is primarily a multiplication of fibromuscular elements. It resembles in its early stages the uterine fibromyoma, which is derived from a muscle cell of the uterus. Since the posterior urethra and the internal vesical sphincter contain muscle fibers which are derived from the same embryologic building material as that of the uterus, it is fair to assume that these two tumors have the same origin. We do not agree wholly with Adrion that the glandular portion of the tumor is necessarily derived from glands but believe that it has its origin in ducts adjacent to the fibromyomatous nodule. The suburethral glands of Albarran are not involved in early lesions. It is probable that the solid nodule produces some stimulating and proliferating effect upon the epithelium of the duct wall, causing the epithelium to invade the solid nodule and form glands within it. The fibromyomatous tissue is invaded and overgrown by a more rapidly growing duct and glandular tissue, with the result that the nodule in its later stages develops the appearance of an encapsulated glandular tumor. Benign prostatic enlargements are not hypertrophies but are true hyperplasias, derived from muscle, fibrous tissue, and ducts.

* * *

Recognition is made of the assistance of Dr. Dan S. Egbert and of Dr. Hyman A. Weiner in the early part of this study. Appreciation is also expressed to Mrs. Ethel Kober for the preparation and mounting of the histologic sections.

The greater part of this work was made possible by an anonymous gift and by a grant from the Fluid Research Fund of Yale University.

REFERENCES

1. ADRION, WALTER: Ein beitrag zur aetiologie der prostatahypertrophie, Beitr. z. path. Anat. u. z. allg. Pathol., 70:179-202, 1922.
2. CABOT, HUGH, and SMITH, GEORGE G.: The influence of stricture of the urethra on the development of hypertrophic changes in the prostate, Lancet-Clinic, 107:456-465, 1912.
3. CIECHANOWSKI, S.: Anatomische untersuchungen über die sogennante prostatahypertrophie und verwandte prozesse. Mitt. a. d. Grenzgeb. d. Med. u. Chir., 7:183-332, 1901.
4. GREENE, R. H., and BROOKS, H.: The nature of prostatic hypertrophy, Jour. A.M.A., 35:1051-1059, 1902.
5. HINMAN, FRANK: The Principles and Practice of Urology. Philadelphia: W. B. Saunders Company, 1935.
6. HINMAN, FRANK, and SULLIVAN, JOHN H.: Two cases of leiomyoma of the prostate. Jour. Urol., 26:475, 1931.
7. HIRSCH, E. W.: Pathology of prostatic hypertrophy. Jour. Urol., 35: 227-234, 1936.
8. KAUSCH, H.: Die prostatahypertrophie. Frankfurt. Ztschr. f. Path., 38: 333-361, 1929.
9. KEYES, EDWARD L., and FERGUSON, RUSSELL S.: Urology. New York: D. Appleton-Century Company, Incorporated, 1936. 6th Edition.
10. LOWER, W. E.: Endocrine influence on male sex organs. New England Jour. Med., 208:878-886, 1933.
11. LOWER, W. E.: The prostatic problem. Jour. Urol., 37:555-556, 1937.
12. LOWER, W. E., ENGEL, W. J., and MCCULLAGH, D. R.: Summary of experimental research on control of benign prostatic hypertrophy and preliminary clinical report. Jour. Urol., 34:670-677, 1935.
13. LOWER, W. E., and HICKEN, N. F.: Experimental research by parabiosis showing hypophyseal-gonadal influence on growth and development of prostate gland. Jour. Urol., 28:601-606, 1932.
14. LOWSLEY, OSWALD S.: The development of the human prostate gland with reference to the development of other structures at the neck of the urinary bladder. Am. Jour. Anat., 13:299-349, 1912.
15. MARION, G.: Hypertrophie de la Prostate. Encyclopédie Française D'Urologie. Tome VI. Librairie Octave Doin, Gaston Doin, Éditeur, 1923.
16. MITCHELL, D. R., and BLAISDELL, J. L.: Leiomyoma of the prostate. Br. Jour. Urol., 5:381, 1933.
17. PATCH, F. S., and RHEA, L. J.: Leiomyoma of the prostate gland. Br. Jour. Urol., 7:213-228, 1935.
18. RANDALL, A.: Surgical Pathology of Prostatic Obstructions. Baltimore: The Williams & Wilkins Company, 1931.
19. REISCHAUER, F.: Über die formale genese der sogennante prostatahypertrophie. Beitr. z. klin. Chir., 160:460-483, 1934.
20. ROTHSCHILD, A.: Ueber die frage der ätiologischen beziehungen zwischen gonorrhoe und prostata hypertrophie. Centralbl. f. d. Krankh. d. Harn- u. Sex.-Org., 15:177-190, 1904.
21. TANDLER, J., and ZUCKERKANDL, O.: Studien zur Anatomie und Klinik der Prostatahypertrophie. Berlin: Julius Springer, 1922.
22. THOMPSON, H.: The diseases of the prostate: their pathology and treatment, comprising the Jacksonian prize essay for the year 1860. 4 ed. Philadelphia: H. C. Lea, 1873.

23. VELPEAU: Leçons Orales de Clin. Chir., Paris, 1841, t. iii, 478. Cited by Crandon, L. R. G., The pathogenesis and pathological anatomy of enlarged prostate. Ann. Surg., 36:846, 1902.

24. VESEEN, L. L.: Fibromuscular hyperplasia of the prostate. Jour. Urol., 22:302, 1929.

25. WALKER, GEORGE: A contribution to the study of the anatomy and physiology of the prostate gland, and a few observations on the phenomenon of ejaculation. Johns Hopkins Hospital Bulletin, II (No. 115): 242-256, 1900.

26. ZUCKERMAN, S., and GROOME, J. R.: The etiology of benign enlargement of the prostate in the dog. Jour. Path. and Bact., 44:113-124, 1937.

RHABDOMYOSARCOMA OF THE PROSTATE IN A BOY SEVEN YEARS OF AGE

REVIEW OF THE LITERATURE

GEORGE GILBERT SMITH, M.D., AND E. ROSS MINTZ, M.D.

Boston, Massachusetts

Sarcoma of the prostate is a relatively rare disease; Gilbert,[6] reviewing the literature in 1934, found only 106 cases reported. According to Smith and Torgerson,[14] it occurs most frequently in the first decade (30.5 per cent) although a few instances occurring in men over fifty have been recorded. The types of sarcoma which have been described are numerous; Randall,[13] in a study of one hundred cases, found fourteen different varieties.

This paper is concerned only with those tumors which arise from striated muscle cells, the so-called rhabdomyosarcomata. In an excellent article dealing largely with the gross and microscopic pathologic changes of this type of tumor, Cappell and Montgomery,[2] of the Pathology Department of the University of St. Andrews and Royal Infirmary, Dundee, classify tumors arising from striated muscle tissue as follows:

A. Those with well-developed cross striations.
   1. Simple rhabdomyomata composed wholly of well-differentiated muscle fibers.
   2. Malignant rhabdomyomata or rhabdomyoma sarcomatodes (a pleomorphic round and spindle cell sarcoma showing well-developed cross-striation in at least a small proportion of cells).

B. Simple myoblastomata, which are composed of myoblasts of spindle shape, taking stains as do muscle tissue, devoid of striations or showing delicate striæ. May be malignant. These myoblastomata are believed by Cappell and Montgomery to be a more embryonic form of the rhabdomyomata.

Costa[3] and McFarland think that the rhabdomyomata should be classified as mixed tumors, not as sarcomas; with this opinion Randall agrees. Most writers, however, believe that since a sar-

TABLE I

Reporter	Age	Duration	Type	Extension	Metastases	Treatment	Complications
1. Socin[15] 1871	26 yrs.	5 mos.	R M S				
2. Kaufmann[10] 1902	9 mos.	7 wks.	R M S	Confined to prostate.	None.	None.	Rt. hydronephrosis. Lt. pyelonephritis.
3. Kaufmann[10] 1902	4 yrs.		R M S	Bladder, post. urethra, both sem. vesicles.	None.	None.	Sup. cystitis with bilateral pyelonephritis.
4. E. Kaufmann[9] 1902	26 yrs.	4.5 mos.	R M S	Bladder, urethra, rectum.	Liver, lungs, kidneys, bones, and stomach.	Not stated.	
5. Greig[7] 1908	4 yrs.	10 mos.	R M S	Not stated.	Not stated.	None.	
6. Squier[16] 1916	40 yrs.	6 mos. +	R M S	Recurrence in scar.	Final result not given.	Total perineal prostatectomy.	
7. Smith & Torgerson[14] 1924	31 yrs.	6 mos.	R M S	Bladder, rectum, urethra.	Lungs, 10th rib, 4th left vertebra.	Perineal prostatectomy	
8. Kretschmer[11] 1926	31 yrs.		R M S	Not stated.	Not stated.	Operation—type not stated.	
9. Holmes Coplan[8] 1930	4 mos.	7 wks.	R M S	Trigone and ureteral orifices.	None.	Cystotomy. Enucleation of prostate.	
10. Katzmann[10] 1931	13 mos.		R M S	Localized to prostate.	None.	Cystotomy.	Died. Pyelonephritis.
11. DeRom & Thomas[4] 1931	23 yrs.	4 mos.	R M S	Not stated.	Osseous—ilium, occiput.	Perineal section. Cystotomy.	
12. Urtubey & Sicre[18] 1933	59 yrs.	Not stated	R M S	Not stated.	Not stated.	Suprapubic enucleation. Cystotomy.	
13. Foucar[5] 1935	26 yrs.	6 wks.	R M S	Trigone, vesicles, rectum.	Lungs, cerv. & med. glands, liver, skull, 12th dorsal vertebra.		
14. Smith 1938	7 yrs.	?	R M S	?	Lungs.	Total prostatectomy, suprapubic.	

coma is a tumor arising from the mesoblast, rhabdomyomata, which arise from the striated muscle fibres of the mesoblast, should be classified as a form of sarcoma. Proust and Vian[12] say that Eberth, in 1872, was the first to detect the presence of striated muscle fibres in a sarcoma of the prostate. His discovery was confirmed by others—Marchand, Kocher and Langhans, Osler, Ribbert, Williams and Brock.

Inasmuch as the demonstration of striations depends upon careful staining technic, it is possible that a number of cases reported as spindle or round cell sarcoma may have been rhabdomyosarcoma, or the more embryonic myoblastoma. Foucar states that rhabdomyosarcomata may arise from the anterior commissure of the prostate, which is composed of dense connective tissue traversed by bands of striated muscle fibres.

We have been able to find in the literature only twelve cases diagnosed as rhabdomyosarcoma; to this list we add one case. A summary of these thirteen cases (Table I) gives the following data: Age of patient. Six patients (46 per cent) were under ten years of age; two of these were under one year (four months, nine months); three were between twenty-one and thirty years, three between thirty-one and forty years, one was fifty-nine years of age.

Local extension was found to occur in six; in two the growth was confined within the prostatic capsule; in five no information as to this point was given. Metastases were present in five and were usually widespread; no metastases were found in four; in four instances, this factor was not determined. Osseous metastases were demonstrated in four patients.

The following operations were carried out:

Cystotomy in three cases.
Total perineal prostatectomy in one case.
Partial perineal prostatectomy in one case.
Suprapubic enucleation in two cases.
Total suprapubic prostatectomy in one case.
No operation in three cases.
Not stated in two cases.

All thirteen patients died of the disease or were obviously facing a fatal termination. In five instances the length of life was not given, but in the eight cases in which it was stated, ten months was the longest.*

Cappell and Montgomery, in a clinical and pathologic study of twenty-two cases of rhabdomyomata occurring in various parts of the body, found four originating in the prostate, four in the spermatic cord or testicle, one in the urinary bladder. Two cases which they reported arose from the soft palate. They also mention ten cases found in the literature of rhabdomyoma of the urinary bladder.

From a study of their own four cases, all of which arose from mucous surfaces, they found that certain characteristics prevailed in all. The tumor grew in a nodular, polypoid form; it was white or flesh-colored and somewhat translucent; it looked soft but was firm to the touch. All four recurred locally; three were known to have produced metastases, one in adjacent lymph nodes and by direct invasion of contiguous tissue, two by both lymph and blood stream.

Rhabdomyoma sarcomatode, these authors say, "differs from other sarcomata in its tendency to dissemination by the lymphatic pathway—in the later stages, widespread blood-borne dissemination occurs, but this may be merely a terminal event."

In the series of twenty-two cases tabulated by Cappell and Montgomery, the tumor spread by lymphatics alone in five instances, by blood alone in five, by both blood and lymphatics in eleven.

The tendency to local recurrence is emphasized by Cappell and Montgomery; this is likely to occur in spite of extensive surgical excision, and may take place even after several years.

The outstanding symptom in sarcoma of the prostate is urinary retention. In a few cases, hematuria was the presenting symptom.

The diagnosis of sarcoma must be made, as Kretschmer[11] points out, by exclusion. The age of the patient (all but one of this series of thirteen occurred in patients under thirty-two years of

*In a case reported by Sysak[11] as rhabdomyosarcoma of the prostate, the major part of the growth lay between the prostate and the rectum, and was separated from the prostate by a capsule of fibrous tissue. There was a nodule of tumor in the left lobe of the prostate, and tumor cells were found infiltrating the musculature of the bladder. In reviewing this case, I did not get the impression that it was primarily of the prostate. It is not included in the above series. The patient died of miliary tuberculosis; no metastasis from the rhabdomyosarcoma were found.

age) excludes carcinoma. Tuberculosis, abscess of the prostate and echinococcus disease must be ruled out. Some sarcomas are soft, some are very firm; apparently it is unusual for them to present the stony induration so characteristic of carcinoma.

The treatment of these tumors by surgical excision has been uniformly unsuccessful. So far as is recorded in the literature, in no case of rhabdomyosarcoma of the prostate was cure effected. Yet four cases are on record in which autopsy failed to show metastases; these patients died from infection of the upper urinary tract. It is conceivable that total prostatectomy might be successful provided the diagnosis were made while the growth was still confined within the prostatic capsule, but the growth of the tumor is so rapid that by the time the diagnosis is made, the chances are overwhelming that tumor cells will already have invaded neighboring structures.

Irradiation, both with radium and deep x-ray, has been employed in various types of sarcoma with some success by Barringer, Bumpus[1] and Young;[20] Gilbert,[6] from a careful review of the literature, concludes that it is far superior to surgery. It is to be noted, however, that the only results at all encouraging were obtained in adults, in whom the tumor may be of slower growth than it is in children. A patient with rhabdomyosarcoma of the nasopharynx was treated by George Tobey and Leroy Schall[18] both with radon implants and the million volt x-ray, but without avail. The tumor was very radioresistant.

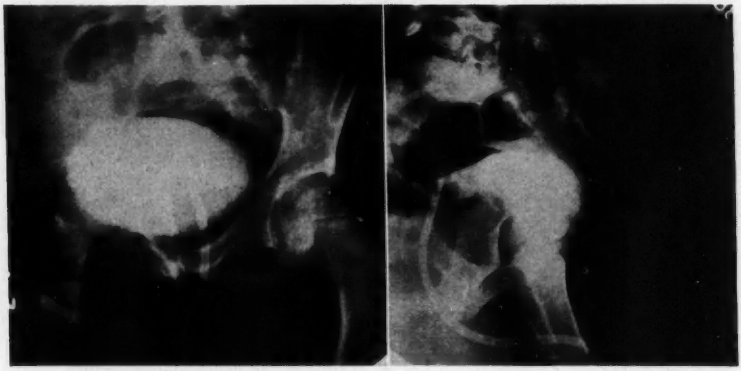
The case which is to be reported illustrates only too well many of the preceding observations.

CASE REPORT

A boy, seven years of age, the son of a physician, entered the Baker Memorial Hospital on January 17, 1938, with a history of complete urinary retention. His parents thought that for several months he had shown some evidence of difficulty in urinating, but the definite history of his present illness began December 28, 1937, when he had trachyitis, coryza and a slight fever. At this time it was noted that he had frequency and urgency of urination; these symptoms increased and on January 10, 1938, he was found to have a distended bladder. He was catheterized and 200 c.c. of urine obtained. From that time until his admission to the hospital a week later, he was almost entirely dependent on catheterization. A catheter had been fastened in the urethra the day before entrance.

There was no history of cancer or tuberculosis in the family. Three other children were in good health. The patient had had a tonsillectomy in 1933, and in May 1934 a peanut was removed from the right bronchus by bronchoscopy. In the past six months, the child had gained more weight and had seemed in better health than ever before.

Physical examination showed a healthy appearing boy, wearing an indwelling urethral catheter. General physical examination showed nothing abnormal except a slight systolic murmur over the cardiac



Figs. 1 and 2. Filling defect in cystogram due to prostatic tumor.

apex and the pulmonary area. No enlarged glands were felt, the kidneys were not palpable and no abdominal masses were felt. Chest roentgenograms revealed no abnormalities. Blood examination showed a leukocyte count of 9,000, red count 4,370,000, hemoglobin 83.5 per cent, polymorphonuclear leukocytes 46, small lymphocytes 38, mononuclears 10, eosinophiles 5 per cent, basophiles 1.7, red blood cells and platelets appear fairly normal. Prolan test was negative. Estrin was negative for 7.7 rat units per liter and over. Blood serum nonprotein nitrogen 29 milligrams per cent.

Rectal examination showed a prostate 4 to 5 centimeters in diameter, rather prominent, firm almost to the point of being hard. The apical and lateral sulci were well marked and the gland was not fixed. The upper border was not clearly defined; the induration extended at least 5 cm. above the perineum.

Intravenous pyelograms showed normal kidney function on both sides; there was no dilatation of pelves or ureters. The cystogram showed a filling defect in the prostatic region, more marked on the left. This defect was irregular and about 3 cm. in greatest diameter

(Figs. 1 and 2). A retrograde cystogram showed reflux of the fluid into the lower portion of the left ureter.

Consultation was held with Dr. Richard M. Smith, Dr. Fuller Albright, Dr. Francis T. Hunter, Dr. Tracy Mallory and Dr. Aubrey Hampton. It was agreed that the prostate was the seat of a tumor, probably some type of sarcoma. Doctor Hampton, radiologist at the Baker Memorial Hospital, was opposed to extensive x-ray treatment because of the effect of the irradiation on the epiphyses of the bones of the pelvic girdle, and because it was not known whether the tumor was of a radiosensitive type.

It was finally decided to give enough treatment to produce a change in the tumor if it were very radiosensitive, such as a lymphoblastoma might be. Four treatments of 300 r. each were given, two anterior and two posterior, to the region of the prostate through a 4 x 5 centimeter field, in consecutive days ending January 21, 1938. The factors of radiation were 200 Kv.P., 40 r per minute, 50 centimeter distance with a filtration of copper ¾ millimeters and 1 millimeter of aluminum.

The condition of the prostate was examined every few days and it seemed to three of us who examined the patient rectally that the gland was reduced in size about 30 per cent. The catheter was removed, but the patient was still unable to void.

On January 31 the patient was examined cystoscopically under gas-oxygen anesthesia. A 16 French observation cystoscope passed easily. The bladder was not remarkable except for some reddening of the mucosa in the base. The ureteral orifices appeared to be slightly dilated. Both lateral lobes of the prostate appeared to be enlarged, especially anteriorly; there was a marked anterior cleft. The internal urethral orifice was patulous; both lateral lobes could be seen to be projecting into the prostatic urethra. Their urethral surfaces were smooth, but where they projected into the bladder they appeared irregular and lobulated. On the left lateral wall of the bladder just above the prostate there was a nodule of pale, watery aspect.

On rectal examination with the cystoscope in place, only a thin layer of tissue lay between the finger and the cystoscope. Lateral to the cystoscope, one could feel masses of tissue. A mass 1 cm. in diameter could be felt above the prostate on the left. An attempt was made to do a needle biopsy through the perineum, but the material obtained contained only blood cells.

It was finally decided to explore the tumor and secure a biopsy specimen.

On February 8, 1938, with the patient under gas-oxygen-ether anesthesia, a median suprapubic incision was made. The outer aspect of the bladder was exposed and the space of Retzius opened freely. From the anterior surface of the prostate, a piece of tissue was removed and a frozen section made, which Dr. Mallory reported as showing a rare form of tumor containing spindle and giant cells, and

probably malignant. As the prostate was freely movable and its capsule apparently intact, it was decided to open the bladder with the idea of removing the entire prostate. Upon incising the anterior bladder wall, a lobulated tumor could be seen projecting into the vesical cavity from the prostatic urethra. The growth extended for perhaps a centimeter along the left lateral wall of the bladder but the trigone was not indurated. The bladder musculature was definitely hypertrophied. The incision was carried downwards on either side, at least 0.5 centimeter above any palpable induration. It was carried across the trigone just below the ureters. The prostate was then freed laterally, the urethra severed between the apex of the prostate and the triangular ligament, and the prostate freed on its posterior aspect from below upwards. It was removed, together with the vesicles (Fig. 3). A 14 French catheter was passed through the urethra

Fig. 3. Vesical aspect of prostate and bladder neck.

and the central point of the trigone sutured with zero chromic catgut to the triangular ligament just posterior to the urethral stump. Two lateral sutures were placed to hold the trigonal edge to the lateral edges of the urethra, and the incision in the anterior bladder wall was closed with a double layer of running catgut sutures. An open-ended mushroom catheter was left in the bladder at the upper angle of the incision and the tip of the urethral catheter brought out through the abdominal sinus. Two cigarette wicks were left in the pelvis, one on each side of the bladder neck. The abdominal wall was closed with two through and through sutures of silkworm gut; the fascia was closed with catgut. Following the operation the child was given a transfusion of 250 c.c. of citrated blood.

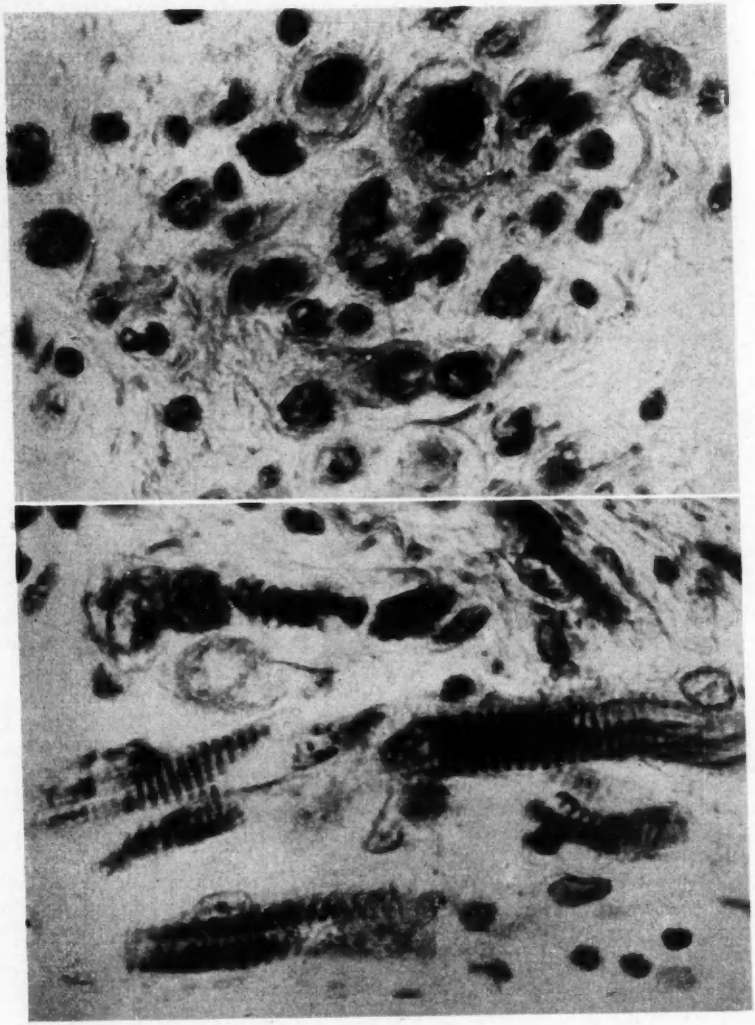
Pathologic Report.—Gross (Bladder, Prostate): A resected prostate, prostatic urethra and neck of the bladder distal to the urethral

orifices. The funnel-shaped portion of bladder mucosa measured 2.5 cm. in diameter. There was moderate edema of the mucosal folds, causing them to protrude inward a distance of 1 cm. and one fold stands out, simulating a papilloma 1 cm. in diameter. The prostatic urethra was normal except for slight congestion. Slight enlargement of the prostate was apparent, its measurements being 5 x 3.5 cm. and its weight 30 grams. The shape was normal. There was a dense, white, homogenous, but soft cut surface. Microscopic: The tumor presented a very pleomorphic appearance, the cells varying tremendously in size and shape. Many of them were broad and elongated and appeared very much like degenerating striated muscle fibers. Others were spindle-shaped, with frayed ends, and still others were round or oval. Most of these round cells were very large, about the size of foreign body giant cells. The cytoplasm was eosinophilic. The phosphotungstic acid hematoxylin stain demonstrated very prominent cross and longitudinal striations in the elongated cells. It also showed interlacing striated fibrils within the cytoplasm of many of the round cells. The nuclei also varied a great deal in size and shape. Many giant forms were seen, but very few mitoses. Some of the cells seen in cross section contained as many as six nuclei, and often these seemed to be arranged around the periphery of the cell (Figs. 4 and 5).

The patient stood the operation well; for eight days his temperature oscillated between 100 and 103, pulse 120-140. There was considerable leakage of urine from the incision. On February 15 the wicks were removed. The temperature again became elevated, due, we thought, to a pyelitis. Prontylin was given for ten days with the reduction of the fever. On March 3 the suprapubic tube was removed and the catheter changed. Rectal examination showed no induration. A cystogram, on March 15, showed a pressure defect at the right side of the bladder neck (Fig. 6). It was thought this might be due to a residual abscess. By March 20, six weeks after operation, the abdominal incision had closed. The catheter was removed. At first, urinary control was absent, but it was quickly regained. Two days later the patient developed a dry cough; a chest roentgenogram showed several round nodules in both lungs (Fig. 7). On March 25 the child was discharged to his home in a neighboring state.

A recent report states that he has had two attacks of fever and has passed thick pus in the urine at times. He complains of pain at the end of urination, but has good control and empties his bladder completely. He is being given x-ray therapy to the chest and to the prostatic region.

This tragic case has run true to form in that the tumor rose from the anterior portion of the prostate, presented a lobulated, white, non-ulcerated surface, and metastasized to the lungs. We do not know whether local recurrence has occurred, but it is to be ex-



Figs. 4 and 5. High power microphotographs from the prostatic tumor.

pected. We still believe that irradiation, either with x-ray or with radium, would have been fruitless. Thorough treatment with radium would have caused great bladder distress, and even if successful in killing the tumor would have left the patient with a cicatrized

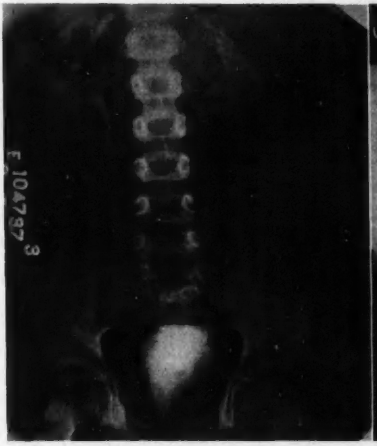


Fig. 6. Intravenous pyelogram five weeks after operation.

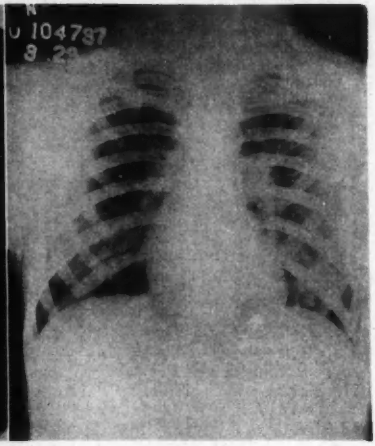


Fig. 7. Lung metastases demonstrated seven weeks after operation.

bladder neck which would have surely caused trouble. Whether the operation that was done will keep the patient comfortable while he lives cannot be answered as yet.*

CONCLUSIONS

1. Rhabdomyosarcoma of the prostate is a rare disease. Twelve cases have been found in the literature, and one case has been added.

2. Forty-nine per cent of the cases occurred in children under ten years of age; all but one occurred in patients under thirty-two years of age.

3. The meager evidence at hand tends to prove that rhabdomyosarcoma is very radio-resistant.

*About five months after operation the suprapubic incision opened and all urine drained in this way. There evidently was local recurrence of the growth. The child died a few weeks later, his death being directly due to increase of the pulmonary metastases.

4. These tumors tend to recur locally, and in the terminal stage metastasize by blood dissemination.

5. No cure has been reported.

BIBLIOGRAPHY

1. Bumpus, H.: Radium and roentgen ray in the treatment of the prostate. Jour. Urol., 14:519-533, 1925.
2. Cappell, D. F., and Montgomery, G. H.: On rhabdomyoma and myoblastoma. Jour. Path. and Bacteriol., 44:517-48, 1937.
3. Costa, A.: Sul Sarcoma Della Prostata. Arch. Ital. di Chir., 21:417-435, 1928.
4. DeRom, F., and Thomas, M.: Sarcome de la Prostate. Ann. et Bull. Soc. Roy. de Med. de Gand., 10:144-152, 1931.
5. Foucar, F. H.: Rhabdomyosarcoma of the prostate. Amer. Jour. Path., 11:753-759, 1935.
6. Gilbert, J.: Sarcoma of the prostate. Jour. Urol., 32:63-77, 1934.
7. Greig, D. M.: A case of rhabdomyosarcoma of the prostate in a child aged four years. Brit. Jour. Child. Dis., 5:185-189, 1908.
8. Holmes, R. S., and Coplan, M. M.: Sarcoma of the prostatic area in an infant of four months. Jour. Urol., 24:539-547, 1930.
9. Kaufmann, E.: In die Verletzungen und Krankheiten der Prostata. By Socin and Burckhardt. Deut. Chir. Stuttgart, 1902.
10. Katzmann, K.: Beitrag zur Kenntnis von Malignen Rhabdomyomen der Kindlichen Prostata. Ztschr. (Frankfurt) f. Path., 41:296-306, 1931.
11. Kretschmer, H. L.: Sarcoma of the prostate. Jour. Urol., 16:301-305, 1926.
12. Proust, R., and Vian, E.: Le Sarcome de la Prostate. Ann. des. mal. des org. Genito-urin., 25:721-728, 1907.
13. Randall, A., and Hughes, B.: A critique of prostatic sarcoma. Tr. Assn. Gen-Urin. Surg., 22:245-260, 1929.
14. Smith, R. R., and Torgerson, W. R.: Sarcoma of the prostate. Surg., Gynec. and Obst., 43:328-337, 1926.
15. Socin, A.: Die Krankheiten der Prostata. Billroth. Pitha. Handb. der Chirurgie III. Bd., Heft 8, 2 Halfte, 1875.
16. Squier, J. B.: Rhabdomyoma of the prostate. Surg., Gynec. and Obst., 23:341, 1916.
17. Sysak, N.: Ein Beitrag zu den Tumoren der Prostata in Kindesalter. Virch. Arch. Path. Anat. u. Physiol., 247:604-612, 1923.
18. Tobey, George, and Schall, Leroy: Personal communication.
19. Urtubey, L., and Sicre, P. L.: Sarcoma Rabdomeoblastico de Prostate en un Suseto de Edad. Avanzada. Arch. Espon. d'oncol., 3:235-243, 1933.
20. Young, H.: Sarcoma of the prostate. Cabot's Modern Urology, Vol. I, 802-805. Philadelphia: Lea and Febiger, 1924.

PROSTATIC CARCINOMA WITH EXTENSIVE INTRAPROSTATIC CALCIFICATION

WITH A DISCUSSION OF THE POSSIBLE RÔLE TO PROSTATIC PHOSPHATASE

BENJAMIN S. BARRINGER, M.D., and H. Q. WOODARD, Ph.D.

From the Memorial Hospital, New York City

This case, if not unique, is certainly rare in the annals of genitourinary diseases, and as such is reported.

The unusual feature is a massive calcification of an extensive prostatic carcinoma. We frequently see osteoplastic metastases from prostatic carcinoma; a metastasis in which bone is laid down. It is for some unknown reason very rare to have calcification within the primary carcinoma itself. There is apparently a direct relation between the laying down of bone in prostatic carcinoma and the blood phosphatase. The determination of the blood phosphatase may have some value in diagnosing osteoplastic metastases, possibly before such metastases are revealed by a radiograph. It unquestionably is of value in the differential diagnosis of the source of a bone metastasis.

CASE HISTORY

F. S., aged fifty-nine years, was admitted to Memorial Hospital on November 18, 1937, with the following history: Previous to the present illness he had had no serious sickness, injury or operation. The present illness began a year before seen, with increasing day and night frequency of urination. In August, 1937, he had complete retention which required catheterization. He had some urgency of urination, but no dysuria, no history of hematuria and no pain referred to his prostate or referable to the distribution of the sacral nerves. He had had no loss of weight. He had some slight loss of strength and no treatment. His nocturia was three to four times when seen. His local physician had made a diagnosis first, of stones of the prostate, and second of prostatic carcinoma. He was very nearly right in both diagnoses.

The examination revealed that the patient had ½ ounce of residual urine and a reasonably clear urine. The rectal examination of the prostate showed it to be very irregular and stony hard. One indurated lump was in the median line directly under the mucosa. There were wide extensions of the induration laterally and up in the region of the seminal vesicles. The topmost part of the induration

could not be palpated. The cystoscopic examination revealed a slight enlargement of the median lobe of the prostate. No lateral lobe hypertrophy. The prostatic margin was smooth and regular, covered with normal mucous membrane. There was no irregularity as is so often seen in prostatic carcinoma.

An aspiration biopsy was attempted, but the aspirating needle encountered stony hardness and no tissue was obtained.

The roentgenologic report was as follows: The appearance of calcareous material in the stereoscopic films made after air injection of the bladder suggested that the process had its origin in the prostate. Its irregularity in outline and density suggested that the process was the result of an extensive infection, inflammation or growth, rather than the ordinary type of prostatic calculus. This is extraordinarily accurate reading of the roentgenogram by Dr. Ralph Herendeen.

There was no evidence of bone metastasis.

The pre-operative diagnosis was massive prostatic stone with possible carcinoma of the prostate.

The patient was operated on November 22, 1937, and a large tumor mass was found in the region of the prostate. It was irregular about 7 x 5 cm., fixed to the surrounding tissue. The bladder mucous membrane over the mass was broken through and the finger encountered a stony hard mass directly beneath. No line of cleavage was found and nothing could be accomplished in attempting to shell out the stony mass; with a large bone rongeur a groove was bitten through the area corresponding to the median lobe, leaving behind a massive tumor mass. A suprapubic tube was inserted and the wound closed.

The pathologic report was as follows: Adenocarcinoma of the prostate Grade III. In addition the "calculus" was surrounded by cartilage and spindle-celled tissue resembling periosteal sarcoma.

In an adidtional note Dr. Stewart says: "Has prostatic phosphatase turned into bone phosphatase?" In a supplementary pathologic report Dr. Stewart says, "Decalcified sections showed the formation of true bone. This bone seems to be a true metaplasia in prostatic carcinoma; that is epithelial bone." The phosphatase examination is included in Dr. Woodard's table.

The patient had an uneventful recovery from his operation. He was given a daily dose of deep roentgen therapy, 400 r., volt 200, ½ mm. of copper, target skin distance 70, port 14 by 11 cm. With two portals of entry anterior and posterior, he was given a total of 3200 r.

At the present time he is urinating well. His wound has closed and he is slowly getting his strength back.

A consideration of the serum phosphatase may throw some light on this case. Serum phosphatase determinations are ordinarily made in an alkaline medium and measure an enzyme with maximum activity at about pH 9.0. The phosphatase of normal

TABLE I

Case	Diagnosis	Metastases to bone	Acid Phosphatase	Alk. Phosphatase	Ratio: Acid Phosphatase Alk. Phosphatase
1	Benign hypertrophy, prostate	None	0.15	2.6	0.06
2	Tuberculosis, lungs, pelvis prostate	Osteoclastic tubercular lesion, pelvis	0.12	3.6	0.03
3	Inflammatory prostatitis; carcinoma prostate	Possible	0.22	3.8	0.06
4	Colloid adenocarcinoma, prostate	None	0.19	3.9	0.05
5	Carcinoma, prostate	Possible	0.11	4.5	0.02
6	Calcified carcinoma, prostate	None	0.20	12.1	0.02
7	Carcinoma, prostate	Osteoclastic	0.28	5.6	0.05
8	Carcinoma, prostate	Osteoplastic, extensive	0.54	24.5	0.02
9	Carcinoma, prostate	Osteoplastic	0.49	5.6	0.09
10	Carcinoma, prostate	Osteoplastic	3.07	9.5	0.32
11	Carcinoma, prostate	Osteoplastic, extensive	7.6	13.2	0.57

bone is an alkaline one, and is thought to be the source of the major portion of the alkaline phosphatase of the serum. Numerous workers have shown that the alkaline phosphatase of the serum is elevated in cases of osteogenic sarcoma, osteitis deformans and carcinoma of the prostate metastatic to bone. Franseen and McLean,[2] Woodard and Higinbotham[6] and others have found abundant alkaline phosphatase in extracts of osteogenic sarcoma and osteitis deformans tissue. Less attention has been paid to acid phosphatase, although Kutscher and Wörner[4] showed that pros-

tate tissue contains a phosphatase with maximum activity between pH 5 and 6. Gutman, Spraul and Gutman[3] confirmed the findings of Kutscher and Wörner, and in addition found that extracts of metastases to bone from carcinoma of the prostate contained both acid and alkaline phosphatase. This suggested the possibility that acid phosphatase might be demonstrable in the serum of patients having bone metastases from carcinoma of the prostate.

Fig. 1. Roentgenogram illustrating the appearance of calcareous material in the prostate after air injection of the bladder.

Such a finding would be of considerable aid in distinguishing prostatic metastases from osteitis deformans which they resemble in roentgenographic appearance. The following is a preliminary report of a study of this question.

The phosphatase activity of normal serum over the pH range from 6.0 to 9.0 was first determined. The technique of Bodansky as modified by Woodard[5] was employed, except that for the lower pH range between 6.0 and 8.0 the veronal buffer was omitted from

the sodium—β—glycerophosphate substrate. Sufficient hydrochloric acid or sodium hydroxide was added to give the desired pH. The pH values of the serum-substrate mixtures were determined colorimetrically, the precision being ± 0.02 pH for the pH range 8.0 to 9.0, and ± 0.10 pH for the range 6.0 to 8.0. The investigation was not carried into systems more acid than pH 6.0, as increasing difficulty was encountered in acid solutions from precipitation of serum protein and from the acid phosphatase of the red blood cells in sera which were slightly hemolyzed. The time of incubation was adjusted to the phosphatase activity anticipated. It was found that, as one proceeded from the more alkaline to the less alkaline substrates, the activity of the phosphatase of normal serum showed the well-known sharp drop from pH 9.0 to about pH 7.0. Between pH 6.7 and 6.1, however, the phosphatase remained approximately constant at a very low level. A pH value of 6.4 was therefore decided upon as the most convenient point for determining the acid phosphatase; the alkaline phosphatase was determined at pH 8.6 as usual.

We have also examined tissue extracts over the entire pH range from 6.0 to 9.0 and found that one normal and one cancerous prostate contained several hundred units of acid phosphatase and only negligible amounts of alkaline phosphatase. In contrast to this, one specimen of osteitis deformans tissue and one specimen of tissue from a giant cell tumor arising on osteitis deformans contained only alkaline phosphatase. In addition we have confirmed the findings of Gutman et al. that metastases to bone from carcinoma of the prostate contain both acid and alkaline phosphatase.

For comparison with the prostate cases we have determined the acid phosphatase of the sera of forty-seven individuals free from prostatic disease. These include five normals, seventeen cases of tumors of the lymphatics, many with bone involvement, five cases of plasma cell myeloma, four of benign bone tumors, five of osteitis deformans, two of hyperparathyroidism, two of undiagnosed bone dyscrasia, three of carcinoma metastatic to bone and four of osteogenic sarcoma. The alkaline phosphatase of these sera ranged from 2.2 to 170 Bodansky units, twenty-two being in the normal range of 5 units or less, and twenty-five being above 5 units. The acid phosphatase varied with the alkaline phosphatase, showing that the alkaline phosphatase was not completely

inactive in the neighborhood of pH 6.4. When the ratio of the acid phosphatase to the alkaline phosphatase was calculated it was found that this had an average value of 0.027, with a range of 0.00 to 0.07. The average for the twenty-six males was 0.030; that for the twenty-one females was 0.024. It is probable that the slightly higher average for males is due to experimental error, and not to leakage of prostatic secretion into the blood. It is evident from these figures that, in a variety of bone diseases unconnected with the prostate, the acid phosphatase of the serum determined by the method described amounts to only about 3 per cent of the alkaline phosphatase regardless of the degree of elevation of the latter.

Some of the patients with prostatic disease present a very different picture, as may be seen from the table. The first five patients, in whom there was no definite evidence of metastases to bone, had normal values for the alkaline phosphatase of the serum, and the ratio of acid to alkaline phosphatase was also normal. The last five patients had known bony metastases, and in all of these the alkaline phosphatase of the serum was raised, the degree of elevation being roughly proportional to the extent of the disease. This is in harmony with the findings of numerous other observers. In two of the cases with metastases the ratio of acid to alkaline phosphatase was normal, in one it was slightly elevated, and in two it was markedly elevated. As far as may be judged from this small series, there thus appear to be two types of metastases to bone from carcinoma of the prostate. One gives rise to excess in the serum of a phosphatase of the type of that originating in bone. The other gives rise to two phosphatases, one resembling bone phosphatase and the other resembling prostatic phosphatase.

We come now to a consideration of Case 6, which was described in detail in the first part of this paper. The alkaline phosphatase of the serum of this patient was 12.1 units, or three to four times normal, while the ratio of acid to alkaline phosphatase was normal. Since there were no known bone metastases nor symptoms suggestive of bone involvement, the excess of alkaline phosphatase presumably originated in the calcified mass in the prostate. As there was no increase in acid phosphatase, the enzyme appears to

have been entirely of the type associated with bone formation. It is therefore suggested that the calcification of this prostate was due to an alteration of the normal prostatic phosphatase to a type capable of producing calcification.

Strict proof of the above hypothesis is lacking, since the calcified tissue was unfortunately not available for examination. It is hoped that in the future it may be possible to examine metastatic tissue from patients both with and without an increase in the acid serum phosphatase, so that the existence of two types of metastases may be either confirmed or disproved. The investigation has been reported in a preliminary form at this time because of its bearing on the unusual type of prostatic carcinoma described, and because it gives promise of being of considerable aid in diagnosis.

BIBLIOGRAPHY

1. Bodansky, A.: Jour. Biol. Chem., 101:93, 1933.
2. Franseen, C. C., and McLean, R.: Am. Jour. Cancer, 24:299, 1935.
3. Gutman, E. B., Sproul, E. E., and Gutman, A. B.: Am. Jour. Cancer, 28:485, 1936.
4. Kutscher, W., and Wörner, A.: Ztschr. f. physiol. Chem., 239:109, 1936.
5. Woodard, H. Q.: Jour. Lab. and Clin. Med., 22:1287, 1937.
6. Woodard, H. Q., and Higinbotham, N. L.: Am. Jour. Cancer, 31:221, 1937.

HISTOLOGIC STUDIES OF THE EFFECT OF IRRADIATION ON HYPERTROPHY OF THE PROSTATE

ROBERT A. MOORE, M.D., EDWARD L. KEYES, M.D., and ALLISTER M. McLELLAN, M.D.

From the Department of Pathology and the Department of Surgery of the New York Hospital and Cornell University Medical College, New York City

Several years ago one of us (Keyes) reported the favorable immediate effect of irradiation in cases of urinary obstruction due to hypertrophy of the prostate. Further observation of these and other cases has not convinced us that his opinion was well founded.

A number of radiotherapists and urologists have reported clinical observations upon the value of x-ray therapy for prostatic retention but such search of the literature as we have made has not disclosed any reports upon the pathologic condition of the prostate after irradiation. As a contribution to the subject we now desire to put on record the pathologic changes noted in prostatic tissue removed at operation from patients that had been subjected to x-ray therapy from one month to two years previously.

That irradiation of the hypertrophic prostate is an accepted procedure is attested by its inclusion in Ira Kaplan's "Radiation Therapy" (1937). He states that x-ray therapy may, by shrinking the prostate, "relieve the condition" sufficiently and permanently. He employs a 200 kilovolt machine with which, through a filter of 0.5 mm. of copper and 1 mm. of aluminum at a target skin distance of 40 to 50 cm., there is delivered a dose of 150 roentgens to two out of five 9 by 12 inch fields alternately, giving three treatments a week until 1,000 to 1,500 r units have been administered. If necessary, he repeats the course after an interval of six to eight weeks.

This seems to be standard practice though some therapists employ but three fields and treat but one of these at a time. The dose per sitting varies up to 300 roentgens and the size of the field and thickness of filter vary.

There is a great diversity of opinion as to the effect of such treatment. K. Abel, for example, reported in 1936 that since

1932 he had not failed to relieve his patients. He had treated sixty-three and followed thirty-five, of whom twenty-six were subjectively well. Among these twenty-six, seven after treatment had a retention of no more than an ounce and a negligible cystitis; seven a retention of no more than two ounces and cystitis but were satisfied with their condition; and two had occasional attacks of retention requiring catheter after one course of treatment but after a second course their residuum was reduced to an ounce and they felt well.

Gonzalez-Martinez reports that relief may be expected when the residuum is no more than 200 c.c., but confesses that some of his patients have been subsequently operated upon. He reports five patients, one of whom was much improved with the residual urine reduced from over 300 to 150 c.c. but who died of intercurrent disease. The remaining four, with lesser residuum, remained well with no attacks of acute retention for ten years.

Barringer, Dean, Herendeen and Duffy, who represent the surgical as well as the radiotherapeutic staff of the Memorial Hospital, reported in 1934 that their early cases showed distinct improvement accompanied by shrinkage of the prostate perceptible to rectal touch but conceded that "It is probable that the only effects of the irradiation in our series are a distinct decrease and control of the edema of the prostate."

Blum, in 1936, stated that in the past twenty-five years he had had occasion to operate upon many patients who had been previously treated by x-ray, not one of whom had been materially benefited. He further noted that so slight is the x-ray effect upon the prostate that enucleation is not rendered more difficult by previous irradiation.

We have searched the literature of the subject in vain for any evidence of the sclerosing effect of x-ray therapy upon the hypertrophic prostate. It would seem that the conclusion of Barringer and his co-workers is generally accepted, viz., that the desired effect is an alleviation of the associated congestion and edema.

One of us (Keyes) has observed that irradiation of the hypertrophic prostate is habitually followed by a palpable periprostatic edema for a few weeks and believes that the tendency to sponta-

neous hemorrhage from the prostate, with or without hypertrophy, in the form of hematuria or hemospermia is diminished by irradiation.

It is generally accepted that too severe irradiation of the hypertrophic prostate may induce such a degree of swelling in the gland as to induce acute retention of urine. Some observers have noted that the irradiated prostate remains scarred to such an extent that subsequent prostatectomy is rendered more difficult. We have not been able to confirm this observation, though we should hesitate to affirm that it would be impossible to induce permanent sclerosis in the hypertrophic portions of the prostate by irradiation. Indeed, it is not possible to assert from the material at hand that our own patients might not have derived more clinical benefit and shown more definite permanent pathologic changes had they been given doses of irradiation larger than about 1,000 roentgens to which their total dose through each of three portals amounted.

CLINICAL MATERIAL

Twelve patients with hypertrophy of the prostate and active symptoms therefrom consulted one of us (Keyes) in the period, three or four years ago, when he was enthusiastic about this method of treatment. They were accordingly submitted to x-ray therapy. Three portals, an anterior, *(A)*, a posterior *(B)*, and a perineal *(C)*, were used. The first two encompassed an area from 10 to 12 cm. square and the latter an area 6 cm. square. From 200 to 300 r (measured in air) were given through each of the portals on successive days until a total dose of about 1000 r through each portal had been given. The tube skin distance was 60 to 70 cm., the kilovoltage 200, the milliamperes 25, and the time of each treatment eight to fourteen minutes. One-half millimeter of copper and 1 millimeter of aluminum were used as a filter.

One patient died of an intercurrent disease within a few months after irradiation. Six patients have required operation within from one month to two years. Prostatectomy was done on five of these patients and no special difficulty was noted in the enucleation of the hypertrophic lobes. They were relieved of their symptoms by operation and are now well. The sixth patient, treated by transurethral resection, is also well, though a postoperative meatotomy was required to cure him. The failure of irradiation to afford

permanent relief of symptoms as well as the patient's acceptance of this failure may be due to a variety of causes, such as the dosage and duration of the irradiation, the subsequent care of the patient and our own waning faith in irradiation therapy for this condition. In general, recurrence or intensification of symptoms persuaded us to advise operation.

The fate of one patient is unknown, since he was unwilling to accept our decision that he required operation because of the recurring attacks of acute retention of urine from which he suffered after irradiation.

Four patients have remained without symptoms sufficiently severe to drive them to operation. One of these has remained in what might be termed stable equilibrium. The prostate, as felt by rectum, is but slightly enlarged, much as it was before irradiation, and the symptoms are unchanged. The residual urine has not been measured and there were no criteria to determine whether or not he was benefited by irradiation. The other three patients had and have huge bilateral enlargement of the prostate that has shown no measurable shrinkage. Yet none of them, in the three years or more since they were irradiated, has had more than slight disturbance of urination, none of them has had acute complete retention of urine, though two of them had such attacks before irradiation. There has been no noteworthy impairment of the renal function and no acute or progressive infection.

What shall we say of these patients? The radiotherapist would perhaps be proud of them. The urologist is merely anxious, just as the surgeon would be over an unoperated appendix. We have the history of a precisely parallel case, a patient who refused irradiation, whose frequency of urination was disquieting, whose prostate was huge, and who, for four years without treatment, has been spontaneously relieved of symptoms but not of the enlargement of the prostate.

CASE REPORTS

Case 1.—A white man, fifty-seven years old, was first seen on November 2, 1932, complaining of frequency for two years. The median sulcus of the prostate was obliterated, but the gland as a whole was only slightly enlarged. There was a residuum of 100 c.c. He refused operation and was not seen again until December

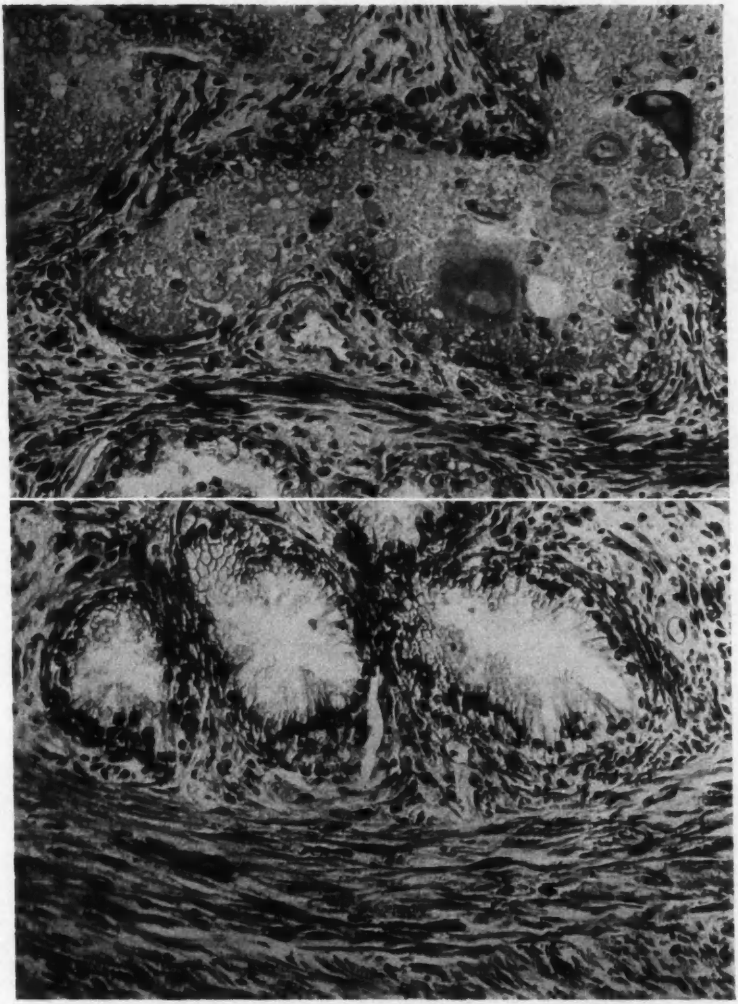


Fig. 1 (*above*). Early degeneration and necrosis of the acinar epithelium in a prostate one month after irradiation. The nuclei are pyknotic and the cytoplasm is granular. There is central swelling of the adjacent muscle cells. (Case 1) ×350.

Fig. 2 (*below*). Periacinar fibrosis. There is a slight increase of the normally thin periacinar layer of collagen. Note that the acinar epithelium is of the typical tall columnar type and that there is central swelling of the muscle fibers. (Case 5) ×320.

9, 1934, when he had an acute urinary infection and epididymitis. The residuum was 30 c.c. and the urine contained many pus cells. He was given x-ray treatment as shown in the accompanying table.

No.	Date	Field	Skin Dose Roentgens	Volt kv.	Cur. ma.	Filter Cu.	Filter Al.	Size Field cm.	T-S Dist. cm.	Time min.
1	12-18-34	A	400	200	25	½	1	10x10	70	16½
2	12-19-34	B	400	200	25	½	1	10x10	70	16½
3	12-20-34	C	300	200	25	½	1	6x6	50	6½
4	12-21-34	A	400	200	25	½	1	10x10	70	16½
5	12-22-34	B	400	200	25	½	1	10x10	70	16½
6	12-23-34	C	400	200	25	½	1	6x6	50	6½
7	12-24-34	A	100	200	25	½	1	10x10	70	6½

There was no improvement and he was admitted to the hospital on January 4, 1935. The prostate was moderately enlarged and elastic. The blood pressure was 180/125. He made an uneventful recovery after a two-stage suprapubic prostatectomy, aside from some mental disturbances that were relieved by psychiatric treatment.

Pathologic Examination.*—The specimen consisted of one mass of tissue which weighed 40 grams. It was firm and nodular and showed a gray, moist, homogeneous cut surface.

Microscopically there were nodules composed only of smooth muscle and others of the usual glandular structure. The glands were lined by a tall columnar epithelium with abundant evidence of secretion. There were occasional acini that showed necrosis of the epithelium and conspicuous central swelling of the surrounding muscle cells (Fig. 1). The remaining stroma contained abundant muscle tissue and there was no fibrosis. There was no lymphocytic infiltration and only a rare small focus of lymphoid tissue.

Case 2.—A white man, sixty-five years old, was first seen on July 6, 1936, complaining of frequency for thirty years. The symptoms had become more severe in the past few months. The prostate was three times normal size and soft. The residuum was 100 c.c. The urine contained no albumin and only a rare pus cell. During July, 1936, he was given x-ray treatment as shown in the accompanying table.

No.	Date	Field	Skin Dose Roentgens	Volt kv.	Cur. ma.	Filter Cu.	Filter Al.	Size Field cm.	T-S Dist. cm.	Time min.
1	7- 7-36	A	400	200	25	½	0	10x10	60	11
2	7- 8-36	C	400	200	25	½	0	10x10	70	14
3	7- 9-36	B	300	200	25	½	0	10x10	60	8
4	7-10-36	A	400	200	25	½	0	10x10	60	11
5	7-11-36	C	400	200	25	½	0	10x10	70	14
6	7-13-36	B	300	200	25	½	0	10x10	60	8
7	7-14-36	A	400	200	25	½	0	10x10	60	11
8	7-15-36	C	400	200	25	½	0	10x10	70	14
9	7-16-36	B	300	200	25	½	0	10x10	60	8

*We are indebted to Dr. N. C. Foot for an opportunity to restudy the sections and prepare additional sections of these cases.

Before the treatment he complained of nocturia, three to four times, and frequency during the day every three hours. Immediately after the treatment the nocturia increased to six times and the frequency to every one and one-half hours. After six weeks the nocturia and frequency were somewhat relieved and the residuum was 30 c.c. On palpation there was moderate edema between the prostate and rectum. On November 19, 1936, the prostate was as large as before treatment, the residuum was 75 c.c., and in view of the continued urinary obstruction he was admitted to the hospital. There was an uneventful recovery after a two-stage suprapubic prostatectomy.

Pathologic Examination.—The specimen consisted of a mass of tissue which measured 6 by 4.5 by 3.5 cm. and weighed 65 grams. On section it was composed of numerous small granular nodules.

Microscopically the nodules were composed of abundant acini lined by a tall columnar luminal layer and a flat basal layer. The luminal cell membrane of the columnar cells was irregular and there was moderate evidence of apocrine secretion. There were abundant papillæ with piling up of the nuclei on the tips of the papillæ. There were occasional areas of metaplasia to a transitional type of epithelium. The stroma contained the normal relative amount of muscle and connective tissue except for an occasional focus of slight fibrosis. There were a few small foci of edema of the stroma. About a rare acinus there was fibrosis of the stroma and slight compression of the lumen. There was a scant amount of lymphoid tissue and lymphocytic infiltration in the stroma. There was an occasional dilated acinus lined by transitional stratified epithelium with a few polymorphonuclear leukocytes in the lumen.

Case 3.—A white man, eighty years old, was first seen on October 9, 1934, complaining of frequency, dribbling and burning on urination. He had noted nocturia of one to two times for years. The prostate was slightly enlarged, elastic and not adherent to the surrounding tissues. The urine contained albumin and pus cells. During the next three weeks he had one attack of acute retention that subsided on local treatment. On November 1, 1934, the residuum was 30 c.c. In November, 1934, he received x-ray treatment to the prostate as shown in the accompanying table.

			Skin Dose					Size	T-S	
			Roent-	Volt	Cur.	Filter		Field	Dist.	Time
No.	Date	Field	gens	kv.	ma.	Cu.	Al.	cm.	cm.	min.
1	11- 3-34	A	400	200	25	½	1	10x10	70	15½
2	11- 5-34	B	400	200	25	½	1	10x10	70	15½
3	11- 6-34	C	300	200	25	½	1	6x6	50	6
4	11- 7-34	A	400	200	25	½	1	10x10	70	15½
5	11- 8-34	B	400	200	25	½	1	10x10	70	15½
6	11- 9-34	C	300	200	25	½	1	6x6	50	6
7	11-12-34	A	400	200	25	½	1	10x10	70	15½
8	11-13-34	B	400	200	25	½	1	10x10	70	15½
9	11-14-34	C	300	200	25	½	1	6x6	50	6

For two weeks following the last treatment the prostate was edematous but by the end of December, 1934, there was a significant decrease in the size of the prostate and urination was more comfortable. During December and January there was a thrombophlebitis of the femoral vein. In February, 1935, the residuum was 25 to 75 c.c. and the urine contained many pus cells. On May 17, 1935, an excretory pyelogram was normal and cystoscopy showed enlargement of the lateral lobes of the prostate and a bar which covered one-half of the trigone. During the summer the residuum rose to 250 c.c. and a transurethral resection was performed on August 14, 1935, ten months after the x-ray treatment. In November there was a residuum of 10 c.c., but the urine contained many pus cells. During the year 1936, the patient complained of increasing irritation of the bladder, frequency every hour and terminal spasm on urination. The meatus admitted only a No. 18 F. catheter and on December 11, 1936, a meatotomy was done. When last seen, in June, 1937, twenty-two months after transurethral prostatic resection, he had no urinary complaints and the urine was free of pus.

Pathologic Examination.—The specimen consisted of a large number of fragments of tissue that together made a mass about 3 cm. in diameter. The fragments were hard, shiny, homogeneous on section, and showed no characteristic markings.

Microscopically some of the nodules showed glands and stroma and others were composed of small myomatous nodules. The epithelium was in two layers with a tall columnar luminal cell and a flat or cuboidal basal cell. The nuclei of the basal cells were small, irregular and highly chromatic. Papillæ were inconspicuous and there was no evidence of secretion. The stroma between the glands contained fewer muscle cells than are seen in the usual case of benign hypertrophy but the fibroblasts were not increased and collagen was not conspicuous. About a few glands the typical thin layer of collagen was notably increased in thickness and partially hyalinized (Fig. 2).

Case 4.—A white man, sixty-one years old, was first seen on November 9, 1927, because of slight difficulty in urination for three years. The prostate was not palpably enlarged and there was no residuum. During the succeeding six years there was slight progressive increase of the urinary symptoms and by July 16, 1933, he complained of frequency every two or three hours during the day and night. The prostate was slightly enlarged and boggy. There was a residuum of 10 c.c. A cystogram was normal. On June 15, 1934, examination showed slight enlargement of the lateral lobes and trabeculation of the bladder with a bar at the urethral orifice. There was no residuum. During December, 1934, he was given x-ray treatment as shown in the accompanying table.

No.	Date	Field	Skin Dose Roentgens	Volt kv.	Cur. ma.	Filter Cu.	Filter Al.	Size Field cm.	T-S Dist. cm.	Time min.
1	12- 3-34	A	400	200	25	½	1	10x10	70	16½
2	12- 4-34	B	400	200	25	½	1	10x10	70	16½
3	12- 6-34	C	300	200	25	½	1	6x6	50	6½
4	12- 6-34	A	400	200	25	½	1	10x10	70	16½
5	12- 7-34	B	400	200	25	½	1	10x10	70	16½
6	12- 8-34	C	300	200	25	½	1	6x6	50	6½
7	12-10-34	A	400	200	25	½	1	10x10	70	16½
8	12-11-34	B	400	200	25	½	1	10x10	70	16½
9	12-12-34	C	300	200	25	½	1	6x6	50	6½

Immediately following the irradiation there was considerable relief of the frequency and he continued improved during 1935. In 1935 he first noted polyuria and examination revealed an elevated blood sugar and the presence of sugar in the urine. The diabetes was controlled by diet. The residuum varied from 0 to 20 c.c. In the first half of 1936, there was a progressive increase in symptoms so that in June, 1936, there was nocturia three to eight times and frequency every hour during the day. The residuum varied from 20 to 100 c.c. On June 12, 1936, eighteen months after irradiation, he was admitted to the hospital for operation. The prostate was slightly enlarged. The blood pressure was 175/100. Three days after admission parts of the median and lateral lobes of the prostate were removed with a punch through a suprapubic cystotomy wound. Aside from a slight febrile reaction after operation he made an uneventful recovery. A follow-up letter in February, 1938, stated that he was well and free of urinary symptoms.

Pathologic Examination.—The specimen consisted of several pieces of tissue, the largest of which measured 10 by 5 by 7 mm. They were firm in consistency and light yellowish brown in color.

Microscopic study was not satisfactory because only one piece of tissue showed a structure characteristic of benign hypertrophy. The remainder was composed of interlacing bundles of smooth muscle, probably from the neck of the bladder. The muscle fibers were swollen, with vacuolization and prominent myofibrillæ. In the piece there were typical acini with tall columnar epithelium and numerous papillæ. There was no fibrosis of stroma and a few muscle fibers showed central swelling and hyalinization.

Case 5.—A white man, seventy-two years old, was first seen in 1930, because of painful urination, which was relieved by the use of urethral sounds. There was no frequency and no palpable enlargement of the prostate. In 1935, the prostate was moderately enlarged and urination was slow but there was no frequency. In view of a severe glaucoma that required operative treatment, a prostatectomy was not done. He was given x-ray treatment as shown in the accompanying table.

No.	Date	Field	Skin Dose Roentgens	Volt kv.	Cur. ma.	Filter Cu.	Filter Al.	Size Field cm.	T-S Dist. cm.	Time min.
1	4-15-35	A	200	200	25	½	1	12x12	70	8
2	4-15-35	B	200	200	25	½	1	12x12	70	8
3	4-16-35	A	200	200	25	½	1	12x12	70	8
4	4-16-35	B	200	200	25	½	1	12x12	70	8
5	4-17-35	C	300	200	25	½	1	8x8	50	6
6	4-18-35	A	200	200	25	½	1	12x12	70	8
7	4-18-35	B	200	200	25	½	1	12x12	70	8
8	4-19-35	A	200	200	25	½	1	12x12	70	8
9	4-19-35	B	200	200	25	½	1	12x12	70	8
10	4-20-35	C	300	200	25	½	1	8x8	50	6
11	4-22-35	A	200	200	25	½	1	12x12	70	8
12	4-22-35	B	200	200	25	½	1	12x12	70	8
13	4-23-35	A	200	200	25	½	1	12x12	70	8

There was moderate relief of symptoms until December, 1936, when, following a severe cold, he developed complete retention of urine and was admitted to the hospital. In January, 1937, a two-stage suprapubic prostatectomy was done. Postoperative recovery was uneventful except for moderate hemorrhage on the sixth day. He was well and free of symptoms in January, 1938.

Pathologic Examination.—The specimen consisted of a bilobed mass of tissue that weighed 60 grams. One lobe measured 4.5 by 5.0 by 3.0 cm. and the other 7 by 2 by 3 cm. On section there were numerous small nodules and an apparent increase of fibrous tissue. A third piece of tissue, measuring 1.5 by 1.0 by 1.0 cm., showed a similar structure.

Microscopically there was an abundant number of glandular acini lined by a tall columnar epithelium. There were only a few papillæ. The stroma comtained the usual amounts of muscle and connective tissue. There were a few foci of edema but no lymphocytic infiltration. About 10 per cent of the muscle fibers of the stroma showed central swelling and hyalinization. The hyaline part of the fiber stained green with the Masson stain and the nucleus was small, irregular and pyknotic (Fig. 3). The smaller arteries and arterioles throughout were thickened.

DISCUSSION

From the histologic study of five cases there is little positive evidence of a significant effect of the x-ray irradiation on the tissues in prostatic hypertrophy. In Case 1, one month after treatment, there is an occasional acinus with necrosis of the epithelial lining (Fig. 1), a finding that is uncommon in the usual case of hypertrophy of the prostate. This epithelial necrosis is associated with notable swelling and hyalinization of the surrounding muscle cells and it is possible that the x-ray irradiation brought about these changes. The central swelling of from 1 to 10 per cent of the

muscle cells (Fig. 3) that was present in all cases is of no significance because it is found in all cases of prostatic hypertrophy. The same is true of the small foci of edema of the stroma. In Cases 2 and 3, the hyaline collars about a rare acinus (Fig. 3) may be a result of x-ray treatment. Hyaline thickening about the glands of the posterior lobe is a common finding in senile prostates, but it is distinctly unusual about the glands of benign hypertrophy at any age.

On the side of negative evidence there is also little of significance. It is possibly important that in none of these five cases is there any more than a minimal amount of lymphoid tissue and lymphocytic infiltration. It is well known that the lymphoid tissue and cells are extremely radiosensitive and it would be distinctly unusual to secure five consecutive cases of hypertrophy of the prostate with only small amounts of the characteristic lymphoid tissue. In view of the well known beneficial effects of x-ray on some infections, it is probably also worthy of note that in only one case, Case 2, is there any evidence of inflammation that is so common in cases of prostatic hypertrophy.

There is no difference in the histologic appearance of the prostate in cases that responded well to x-ray treatment (Cases 2, 3, 4 and 5) and in the case that derived no benefit (Case 1). It is possibly significant that in Cases 2 and 3 there was post-radiation edema of the prostate and on section, four and ten months later, there are hyaline collars about a few glands. This is in contrast with Cases 4 and 5, which showed no conspicuous edema and no hyaline collars. In none of the cases is there any fibrosis of the stroma nor any histologic appearance that may be interpreted as evidence of destruction of acini.

These histologic findings emphasize the attitude that has been taken by the more conservative urologists and therapists, namely, that with doses up to 1,000 r no permanent effect on the tissues in prostatic hypertrophy should be expected, but rather only a decrease in the degree of edema and inflammation. Thus x-ray therapy is not to be regarded as a substitute for prostatectomy or resection but only as a form of local treatment in selected cases.

SUMMARY

Of twelve cases of prostatic hypertrophy treated by x-ray irradiation, six required prostatectomy within two years, four were

either improved or in equilibrium with the disease after three years, one died of an intercurrent disease, and the fate of one is unknown.

The prostate in five cases has been studied histologically and there are only minimal changes that might be attributed to x-ray irradiation. These are slight periacinar fibrosis and a relative absence of lymphoid tissue and evidences of inflammation.

BIBLIOGRAPHY

ABEL, K.: Die Röntgentiefenbestrahlung der Prostatahypertrophie. Beit. z. klin. Chir., 164:396-400, 1936.

BARRINGER, B. S., DEAN, A. L., HERENDEEN, R. E., and DUFFY, J. J.: Roentgen treatment of benign hypertrophy of the prostate gland. Am. Jour. Roentgenol., 31:350-355, 1934.

BLUM, V.: Fortschritte und Wandlungen in der Behandlung der Prostatahypertrophie. Med. Klinik, 32:111-115, 1936.

GONZALES-MARTINEZ, I.: Progress, indications, technic, and successful results of radiotherapy in prostatic hypertrophy. Radiology, 24:66-73, 1935.

KAPLAN, I.: Year Book of Radiology, 1932-33, edited by C. A. Waters and I. I. Kaplan, Year Book Publishers.

KEYES, E. L., and FERGUSON, R. S.: Urology. New York: Appleton. Sixth Edition, p. 352.

FACTORS TENDING TO MINIMIZE THE PROSTATECTOMY HAZARD

WITH PARTICULAR REFERENCE TO WOUND ANTISEPSIS

EDWIN DAVIS, M.D.

Omaha, Nebraska

The average individual has a very natural dread of prostatectomy. The average physician or general surgeon has no real conception of the safety with which this procedure may be carried out via the perineal route. I presume to carry this statement even further, by suggesting that probably only relatively few in a select audience of urologic surgeons have a full realization of the opportunity for precision and accuracy which this procedure affords, and recognize the almost complete elimination of hazard which is possible.

At the present time, my own perineal prostatectomy mortality rate, in a series previously reported upon a number of occasions, and now totaling 741, is 2.7 per cent. Every post-prostatectomy death, from *any* cause whatever, prior to dismissal from the hospital has been counted.

This record includes two consecutive series, totalling 121 and 107 respectively, each without a single death. There has been but one death in the last 144 consecutive cases. These figures are mentioned merely as a matter of record, and with no purpose other than to emphasize the possibilities resulting from systematic elimination of the various hazards. Others, particularly Young,[10] Hinman,[8] and Cecil,[1] have reported comparable figures; in fact, better figures. There is no reason why a limited few should have a monopoly on perineal prostatectomy, since the technic may be mastered by anyone with moderate skill and sufficient determination and patience. Young[10] has mentioned that four successive residents at the Brady Urological Institute performed 190 consecutive prostatectomies upon unselected patients from public wards with only three deaths (1.5 per cent).

Amazing though this statement may seem, there is no reason why the mortality rate of perineal prostatectomy in the aged

and debilitated should not be made to compare favorably with that of herniotomy in the young and robust.

My present purpose is to enumerate and to discuss briefly the various factors which are responsible for this conspicuously low mortality rate, and which would seem to have placed perineal prostatectomy in the category of so-called "finished" operations. This term seems permissible, because (1) the mortality rate so closely approximates the "normal" death rate* at the age of seventy, and because (2) questionnaire records (Davis[3]) show that, of these aged individuals, many of them with unrelated ailments and symptoms which might readily be confused, 82.3 per cent voluntarily classify themselves as "well," and 98.8 per cent "well or improved."

The lowering of the mortality rate has been essentially a process of elimination of the various hazards, one by one. The chief prostatectomy hazards, together with the "remedy" or method of control of each, are listed in Table I.

TABLE I. FACTORS TENDING TO MINIMIZE THE VARIOUS PROSTATECTOMY HAZARDS

HAZARD	MINIMIZED BY
Uremia	Pre-operative drainage.
Infection	Oral and wound antisepsis. Dependent drainage.
Immediate hemorrhage	Perineal hemostatic bag. Visualization of field and suture-ligature.
Delayed hemorrhage	Endoscopic fulguration. Oral and wound antisepsis.
Anesthesia	Sacral block method. Avoid veins.
Abdominal distention	Perineal route.
Postoperative "shock"	Perineal route. Sacral block anesthesia.
Epididymitis	Vasectomy, preceding preliminary drainage.
Vascular "accidents"	(Prayer)

Uremia.—As known by everyone (but ignored by many), the answer to the uremia question is pre-operative drainage, by retention catheter or via the suprapubic route, for days, weeks, or many months, insistently and inexorably carried out, for as long as may be necessary, regardless of urging to the contrary by patient, relatives, or physician. The surgeon has but few privileges, but one of these is to decline to operate. The necessity for adequate drainage is too well understood to require further comment. I

*According to the American Experience Tables of Mortality, of one hundred individuals alive at seventy years of age, six may be expected to die before reaching seventy-one. Carrying this comparison to its extreme in absurdity, if the period of hospitalization for prostatectomy were one year, the "normal" death rate might be said to be more than twice the post-prostatectomy death rate.

might as well seriously discuss the advisability of hemostasis. There is very little excuse for a post-prostatectomy uremia death.

Infection.—A brief discussion of post-prostatectomy sepsis, together with the presentation of a method tending to decrease this hazard, is the chief occasion for the presentation of this paper.

Prostatectomy without infection of the urinary tract is impossible. In fact, a period of fever during the time of preliminary drainage is decidedly the rule, rather than the exception, and is to be welcomed, by reason of the immunity supposedly conferred. At any rate, high postoperative temperature reactions are relatively far more frequent among those who have not gone through a period of pre-operative fever. Time, and the natural processes of immunity, with the aid of free dependent drainage, tend automatically to take care of these urinary tract infections. In fact, excepting the debilitated, and excepting patients with additional urinary tract lesions, gross pyuria ordinarily disappears spontaneously, after a several week interval following perineal prostatectomy.

Post-prostatectomy *systemic* infection, however, is a different matter. I refer to the occasional occurrence of postoperative bloodstream invasion, characterized by chills, high temperature and evidence of sepsis, and have in mind three post-prostatectomy deaths directly attributable to this cause. Were evidence of blood stream invasion necessary, it might be stated that one of these patients developed multiple small staphylococcus abscesses, distributed over the trunk and extremities.

In that the assumption seemed permissible that such systemic reactions are due to the liberation of virulent bacteria into fresh "unvaccinated" tissues, an attempt at wound antisepsis during operation was considered to be worth the effort. With this thought in mind, a routine surgical technic was adopted, including irrigation of the urethra and bladder with 2 per cent mercurochrome, alcohol and acetone solution (Scott and Hill)* immediately before incision, and flooding the wound with the same solution immediately before closure. Wound sterilization was not expected, but wound antisepsis, with a consequent decrease in numbers and virulence, or in the "dose" of bacteria to which fresh tissues were exposed, was hoped for. This technic was started in January, 1932, although I have since discovered that a similar method had been

employed by Harris[7] in suprapubic prostatectomy, and reported favorably upon as early as November, 1931.

Permitting the assumption that the temperature is a reliable index of the degree of sepsis, it may be said that this technique has given distinctly beneficial results. Moreover, there have been no more deaths directly attributable to sepsis, such as had previously occurred. This improvement may be graphically demonstrated.

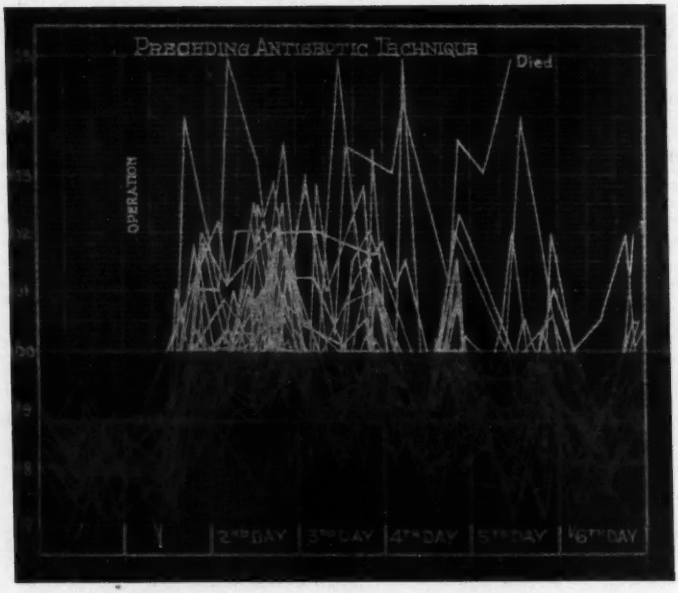


Fig. 1. Superimposed temperature curves of twenty-five consecutive cases of perineal prostatectomy, *preceding* antiseptic technic.

Figures 1 and 2 represent the superimposed temperature curves of the first postoperative week of twenty-five cases of perineal prostatectomy, immediately preceding and immediately following the adoption of the new technic. For the purpose of clearer demonstration, that portion of either chart below 100 degrees has been purposely blurred, thus rendering the elevations relatively more conspicuous. In the chart representing superimposed temperature curves prior to the adoption of the new technic (Fig. 1) the

excess of rulings or lines above the 100 degree level (as compared with Figure 2) is too conspicuous to require further comment.

Figure 3 represents an arithmetical, rather than a graphic method of demonstration that the mercurochrome technic has resulted in a flattening of the average post-prostatectomy temperature curve. These two curves (Fig. 3) represent an accurate portrayal of the average temperature reactions of the two series of twenty-five

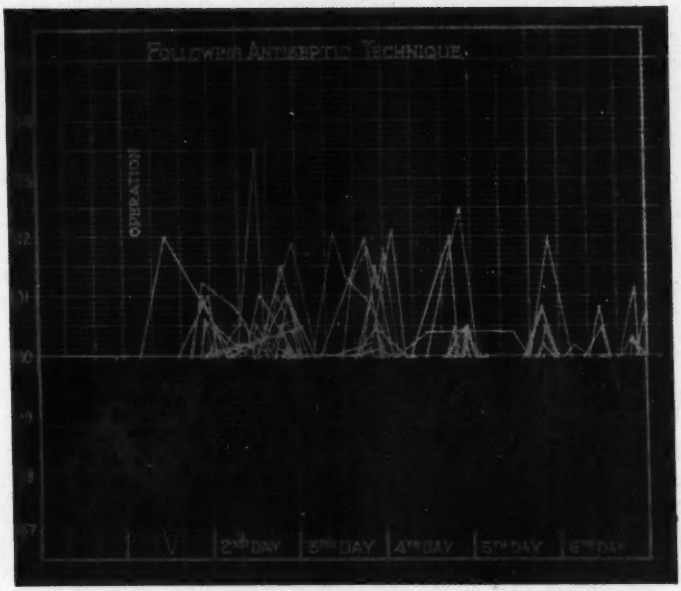


Fig. 2. Superimposed temperature curves of twenty-five consecutive cases of perineal prostatectomy, *following* antiseptic technic.

cases (before and after the new technic), during the first post-operative week. The method of computing was merely to average the maximum daily temperature reading for each of the twenty-five cases. The difference in the two curves is too striking to be ignored. Whereas, the average maximum post-prostatectomy temperature elevation preceding the mercurochrome technic was 101.5°, the average maximum elevation following the institution

of the new technic was only 100.2°. It may be stated that the average maximum elevation occurs on the day following the operation.

Upon the suspicion that the figure is 100.2°, being an average of only twenty-five cases, might not be truly representative, an additional seventy-five cases were added, bringing the total upon which the average was based up to 100. Upon this basis, the average maximum post-prostatectomy temperature elevation was found to

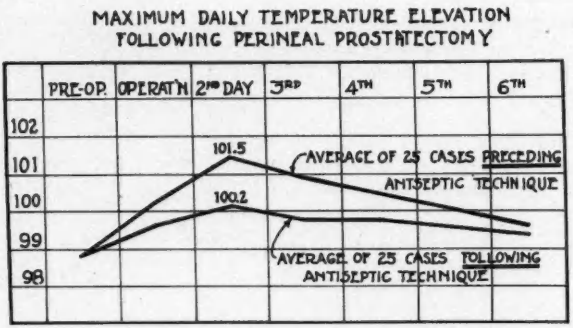


Fig. 3. The average maximum daily temperature elevation of two series of twenty-five cases of perineal prostatectomy, preceding and following the antiseptic technic.

be 100.6° rather than 100.2°. Considering the large number of consecutive cases entering into this tabulation, there can be no question as to the accuracy of the latter figure.

Without undue enthusiasm, it seems permissible to state that any method of wound antisepsis, causing a flattening of the post-prostatectomy temperature curve, may be regarded as another additional factor tending to lessen the hazard of prostatectomy. This preliminary report is purely tentative. It is quite possible that another drug, or a variation of the technic here suggested, might be far more efficient. It is likewise true that a modification of this method might be applicable in other surgical fields.

Immediate Hemorrhage.—A combined hemostatic and drainage bag, for perineal prostatectomy, was presented in 1927 (Davis).[4] This bag has proved effectual in all but four cases out of 741 (99.5 per cent), occurring early in the series, in which emergency suprapubic cystotomy, with suture-ligature, became necessary.

There was one death directly attributable to hemorrhage. Later in the series, it gradually became apparent that additional time and effort devoted to suture-ligature through the perineal incision, at the time of operation, tends to eliminate even this small percentage of hemorrhage. There is no reason why the matter of hemostasis need be left to chance, even in the slightest degree. In that the patient is comfortable and free from pain, there is no necessity for haste. As repeatedly observed through the perineal incision, such arterial bleeding as there may be comes chiefly from tissues underneath the "floor" of the bladder, rather immediately adjacent to the orifice. The main spurters tend to have an anterior, rather than a posterior location, and tend to occupy approximately "ten o'clock and two o'clock" positions with respect to the vesical orifice. Using the inflated bag within the bladder as a tractor, the bladder "neck" may be pulled down and the under surface clearly visualized and made accessible. Each portion of the under surface of the bladder neck may be inspected in turn by varying the direction of the traction upon the hemostatic bag. An excellent opportunity for visualization and suture-ligation of spurters is thus afforded, after which a "pucker" suture is placed upon either side, compressing the relaxed tissues of the two lateral cavities, and closing the capsule. This technic practically eliminates the immediate post-prostatectomy hemorrhage hazard.

Delayed Hemorrhage.—In 1932, I called the attention of this audience to an "epidemic" of delayed massive post-prostatectomy hemorrhage, occurring from the tenth to the twenty-fifth post-prostatectomy day, and suggested an explanation upon a specific infection basis (Davis[5]). This same communication included a method of control consisting of endoscopic aspiration of clots, followed by location and fulguration of the bleeding point. This was long before the advent of endoscopic resection. The "epidemic" consisted of the amazing number of five cases of delayed massive hemorrhage, out of thirteen consecutive prostatectomies, three of these in direct succession as contrasted with only ten cases of delayed hemorrhage in the preceding 410 prostatectomies, thus permitting no conclusion as to etiology other than upon a specific infection basis. In that this complication has not been observed for a period of years, it may well be that the wound antisepsis technic described

above has been a factor in its control. It may also be that one of the newer internal urinary antiseptics (mandelic acid or sulfanilamide) will prove to be of value in this respect. At any rate, it may be conservatively stated that endoscopic fulguration and antisepsis have eliminated the real hazard connected with delayed hemorrhage.

Anesthesia.—The sacral block method, described as applied to perineal prostatectomy in 1922 by Crowell and Thomson,[2] has given complete satisfaction throughout the years, and leaves nothing to be desired. There have been no deaths attributable to the anesthesia, no complications, and no sequelæ. In 1931, a publication (Davis[6]), referring to the "infallibility" of the sacral block method, reported a consecutive series of 229 cases without a single anesthesia failure. This number has since been increased to 592, still without a failure. Sacral block anesthesia in perineal prostatectomy, properly administered, is literally infallible. Moreover, adequate time, permitting deliberateness in hemostasis, is afforded. I consider the sacral block method ideal for the specific purpose of perineal prostatectomy.

Abdominal Distention.—This postoperative complication, so frequently the cause of distress and calamity, following abdominal or suprapubic incisions, is conspicuously absent following the perineal approach to the prostate. There was only one case in the entire series in which abdominal distention occasioned any real trouble.

Postoperative "Shock."—This term is here loosely employed to designate that condition of semi-consciousness or unconsciousness, together with lowered blood pressure and increased pulse rate, in which the patient is returned to his room following many (if not most) major operations. Following the perineal approach to the prostate, under sacral block anesthesia, the patient returns to his room in the same condition with respect to color and general appearance as preceding the operation. I have frequently observed these old men reading or writing the same morning following operation. Whatever "shock" is, this condition is conspicuously absent following the sacral block method, and the perineal approach.

Epididymitis.—Suppurative epididymitis, with chills, fever, and sepsis, occurring as late as (or later than) the third postoperative

week, was frequently a far more serious matter than the prostatectomy. Routine, local infiltration vasectomy, performed at the *beginning* of preliminary drainage, has practically eliminated epididymitis.

Vascular "Accidents."—Such occurrences as cerebral or coronary thrombosis, or pulmonary embolus, suddenly interrupting an otherwise smooth convalescence, are neither to be anticipated nor prevented. Fortunately such "accidents" are rare. It is likely that most of these cerebral and coronary affairs are coincidental occurrences, wholly unrelated to the operation.

CONCLUSIONS

Mercurochrome "wound antisepsis" during perineal prostatectomy tends to flatten out the postoperative temperature curve, and therefore may be presumed to lessen the infection hazard.

Of the various perineal prostatectomy hazards, including uremia, infection, hemorrhage (immediate and delayed), anesthesia complications, epididymitis, and vascular "accidents," all but the last-named are controllable and have been reduced to a negligible minimum.

As determined by tabulating the maximum daily postoperative temperature elevations, occurring after one hundred consecutive cases of perineal prostatectomy, the average maximum elevation, (which occurs on the day following operation) is only 100.6°.

REFERENCES

1. Cecil, A. B.: Pre-operative treatment of prostatic obstruction. Surg., Gynec. and Obst., 58:630, (Mar.) 1934.
2. Crowell, A. J., and Thomson, R.: Sacral anesthesia in perineal prostatectomy. Jour. Urol., 8:81, (July) 1922.
3. Davis, Edwin: Analysis of results in 378 consecutive cases of perineal prostatectomy. Tr. Am. Ass'n G.-U. Surg., 24:387, 1931.
4. Davis, Edwin: Distensible bag for hemostasis and drainage following perineal prostatectomy. Jour. Urol., 18:201, (Aug.) 1927.
5. Davis, Edwin: Massive secondary post-prostatectomy hemorrhage controlled by endoscopic fulguration. Jour. Urol., 28:365, (Sept.) 1932.
6. Davis, Edwin: Sacral block anesthesia in perineal prostatectomy—Its infallibility when accurately administered. Jour. A.M.A., 97:1771, (Dec.
7. Harris, Augustus: The prevention of infections in prostatectomy. Amer. Jour. of Surg., 14:480, (Nov.) 1931.

8. HINMAN, FRANK: The modern operation of plastic perineal prostatectomy. Tr. Am. Ass'n G.-U. Surg., 30:265, 1937.

9. SCOTT, W. W., and HILL, J. H.: Presentation of a pre-operative skin disinfectant, an alcohol-acetone aqueous solution of mercurochrome. Jour. Urol., 14:135, (Aug.) 1925.

10. YOUNG, H. H.: Surgical treatment of prostate. Jour. A.M.A., 110:280, (Jan. 22) 1938.

DISCUSSION

DR. BENJAMIN S. BARRINGER (New York, N. Y.): I would like to discuss Dr. Smith's paper. I have had one case of leiomyosarcoma, and I know Dr. Stevens has had one case. I have had the chance of looking over his case. Now I don't know what in the prostate begets rhabdomyosarcoma and what begets leiomyosarcoma, but as far as I know, they are very much the same.

The case that I had I am going to report in the future. It was a case of man between fifty and sixty. He had a prostatic tumor that when removed was found to be leiomyosarcoma. It recurred almost immediately and was radiated. The tumor was radio-insensitive, very much as Dr. Smith's case, only my patient was a middle-aged man while Dr. Smith's was a young boy; I should say the two are very much the same type. That is, they were as insensitive to radiation as a carcinoma of the prostate. My patient lived between five and six years, and I think he died of pyelonephritis, not, as far as I could see, from his tumor. These cases are not at all like the usual run of what we call sarcoma of the prostate, which is radio-sensitive, grows to enormous size and kills rapidly. It is evidently a different type.

DR. ROBERT A. MOORE (New York, N. Y.): If I may be allowed, Mr. President, I ask your indulgence for a moment for some comments from the standpoint of pathology on Dr. Deming's report. We have been engaged in a similar study for some years and have come to the same conclusion that Dr. Deming has concerning the primary lesion of the benign hypertrophy; that is, it is a proliferation of a peculiar cell in the peri-urethral and perirectal tissue. The nature of this cell is difficult to determine. Dr. Deming has told you that sometimes it stains with the various stains as though it were fibrous tissue and at other times it stains as though it were muscle.

The photomicrographs which he has shown of the epithelium around these lesions are most interesting. In practically every nodule of benign hypertrophy there is a gland about the outside that may be called an encircling gland. The epithelial cells on the

inside are tall and thrown into papillæ and the epithelial cells on the outside are low cuboidal or flat. That seems to us to be the proof that the primary lesion is a stroma hyperplasia and that the glands become secondarily involved in the process. If we are to search for the cause of benign hypertrophy we must search for a substance which causes hypertrophy and hyperplasia of the stroma of the prostate.

I would, however, like to take issue with Dr. Deming on one point, and that concerns the matter of the eunuch and the eunuchoid. I am quite aware of Dr. Deming's own report of prostatic hypertrophy in a eunuchoid. However, in the pathologic literature, which I have gone over with some care, there are twenty-eight cases of eunuchs and eunuchoids proven at autopsy in which there was a gross and microscopic examination of the prostate. In not a single case in that literature was there any evidence of benign hypertrophy of the prostate. All of these men were over forty years of age, and the incidence at autopsy of benign hypertrophy of the prostate makes it a statistical impossibility to have twenty-eight consecutive cases without a single example of benign hypertrophy.

I have therefore concluded, somewhat at variance with Dr. Deming, that benign hypertrophy of the prostate cannot exist without the presence of the testes. What it is in the testes that brings it about I don't know, but I believe the pathologic literature is reasonably clear on the one point.

Dr. Clyde L. Deming (New Haven, Conn.): I appreciate Dr. Moore's discussion and his criticism. If one considers a large number of prostates in men past fifty, one finds that in quite a percentage (at least 50 per cent of our group of 150 cases) there is no evidence of pathologic change, so that we had to hunt or select our cases rather carefully in order to study the microscopic small lesions.

I haven't had any experience with eunuchoids, I only give you the literature, and if the literature is wrong, I am the first one to accept a correct viewpoint with regard to this lesion.

Dr. Barringer: Could we be told the difference between a eunuch and a eunuchoid?

DR. MOORE: The eunuch has no testes at all. The eunuchoid has a demonstrable testes which has apparently never functioned.

DR. DEMING: Whether these epithelial buds are from glands or from ducts may not make any great difference, but in our studies we thought they were from ducts rather than from glands, reverting back to the embryology of the development of the prostatic buds, the prostatic ducts and the prostatic glands as arising from the epithelium of the posterior urethra. We felt that was a more logical conclusion with regard to the development of glandular structure.

DR. BENJAMIN S. BARRINGER (New York, N. Y.): I think we are greatly indebted to Dr. Moore for coming here and presenting his excellent paper. I was interested in this subject some time ago and did about forty consecutive cases of deep x-ray therapy. I realize that the only result was the effect of the x-ray on the edema of the prostate. I think we are very much indebted to Dr. Moore for giving us a nice pathologic report on these prostates.

DR. MOORE: I think, in answer to the question raised concerning hemorrhage, there was no unusual immediate hemorrhage. It was Dr. McLellan's opinion that these prostates were removed without any unusual difficulty.

DR. HOWARD: Did it decrease the amount of hemorrhage?

DR. MOORE: No, in one case there was slight secondary hemorrhage.

URINARY STONE: SOME PRESENT-DAY CONCEPTS*

WILLIAM C. QUINBY, M.D.

From the Urological Clinic of the Peter Bent Brigham Hospital, Boston, Massachusetts

Though the occurrence of calculi in the urinary passages has been noted since the earliest medical records, and the disabilities caused thereby have called forth innumerable efforts toward relief by each succeeding generation of surgeons, it is only of very recent years that medical science has been able to bring forward any reliable data tending to explain firstly *why* calculi form and secondly *how* they form. During the past ten or fifteen years, however, new concepts have appeared, themselves leading to a number of exact observations which in turn have thrown real light on some of the many aspects of this intricate subject. Therefore, a report of progress may be found opportune.

The suggestion that urinary calculi may be caused by the ingestion of improper substances or by taking too large an amount of substances otherwise harmless is of great antiquity as seen in the many writings on the relation of stone to various forms of diet or of waters. Such ideas far antedated knowledge of what we call metabolism today and were based wholly on supposititious cause and effect. But, however lacking in scientific bases such ideas may have been, there remain today two incontrovertible facts out of the mass of conjecture. First, there are regions in the world in which calculous disease is so prevalent as to be truly endemic, and second there are races such as certain blacks in South Africa in whom this disease practically never occurs. Throughout other portions of the globe stone formation varies in incidence, both in place and in time, and quite recently there is reported on good authority a striking wave of increase of lithiasis in Central Europe. Insurance statistics quote a mortality rate of from three or four to as high as twenty-five per million deaths in various countries or in parts of the same country.

Such facts as these make it immediately evident that the problem of calculous disease is composed of many elements, and that we

*Presented before the 16th Congress of the American Physicians and Surgeons.

must expect to deal with varying biologic and chemical conditions and interactions in trying to solve its causes. But, except for such general information as above, nothing remains out of the past, of scientific value today.

At about the end of the first decade of the present century there appeared several new concepts in physiology and in physiologic chemistry which have greatly influenced medical and scientific knowledge, giving us firm ground for the first time for the explanation of many phenomena which had before been obscure or lacking proper correlation. I need only mention here such epoch-making contributions as those of L. J. Henderson on "The Blood" and on "The Fitness of the Environment," and the charmingly convincing ideas of W. B. Cannon related in his book on "The Wisdom of the Body." Here are discussed *in extenso* the factors, physiologic and chemical, which maintain the marvelous stability (homeostasis) of the various bodily systems, especially that of the blood—a stability continuously necessary for existence of the human body. To be added to these more general writings are those of such men as Cushny who has given us the present theories of "The Secretion of Urine" followed by the more specific contributions of van Slyke and Richards. To all this has been added the new knowledge of the vitamins especially at the hands of Mendel, Collip, Wolbach, and many others, as well as contributions on the surprising action of various of the endocrine glands, as found in the instance of the parathyroids, by the investigations of Aub, Bauer and Albright.

These newer concepts point out clearly the extreme importance of physiologic and chemical stability of all bodily systems, demonstrating clearly the methods of various sorts—chemical, nervous or other—by which this stability is maintained under the various stresses and demands made from time to time by the changing external and environmental needs.

As described by Cannon:

> "The coördinated physiologic processes which maintain most of the steady states in the organism are so complex and so peculiar to living beings—involving, as they may, the brain and nerves, the heart, lungs, kidneys and spleen, all working coöperatively—that I have suggested a special designation for these states—homeostasis. The word does not imply something set and immobile, a stagnation. It means a condition—a condition which may vary, but which is relatively constant."

He then discusses the fluid matrix of the body—the blood, lymph, and cellular fluids—the constancy of the water and salt content of the blood—the homeostasis of blood sugar, proteins, fat, and calcium, and the remarkable delicacy of the bodily arrangements for maintaining the neutrality of the blood.

When applied to such a phenomenon as the occurrence of a stone in a kidney such physiological knowledge as this furnishes the fundamental concepts with which any explanation of this occurrence must be in agreement. One may fairly argue as follows: A stone is not a foreign body—except possibly in the surgical sense—for it is made up of substances all of which are present in the blood stream is one form or another. We know, however, how absolutely important for health is the constancy of the blood stream in a chemical as well as a physical sense, that is, its neutrality. We have learned also something of the influence of the kidney in helping to maintain this constant state of the blood by acting as an excretory organ. It follows that at one time or another and under very varying conditions of the general body, substances will be presented to the kidney for elimination now in large amount, now in small, and frequently associated with marked differences in the amount of fluid in which they are dissolved. And even though at times, given the presence of some condition acting as a *nidus* on which crystals may be deposited, such substances are found to have changed their physical state from being in solution to that of precipitation after reaching the spaces of the kidney itself, still at all events the homeostasis of the blood stream has been maintained.

For an explanation of the actual chemical conditions within the kidney itself leading to the formation of a calculus we must look to physical chemistry; and here, though there exists a certain amount of knowledge on the interactions of crystalloids and colloids, or on the influence on the solubility of one substance of the presence of another, exact observations applicable to any single instance await future discoveries. The one certain fact underlying all others is that some condition or substance must exist within the kidney, which will serve to initiate the crystalline deposits which eventually form the stone.

The substances of which calculi are composed are rather sharply divided into two groups: *The smaller* (1) derivatives of proteins

as cystine, xanthin, and uric acid; *the larger* (2) substances containing calcium in some combination such as calcium and magnesium with phosphorus or in combination with oxalic acid, as calcium oxalate.

We have no exact knowledge concerning the causation of the first group—only theories, which cannot be profitably discussed here. There is more to be said for the calculi containing calcium in some form as this is one of the elements of the body in regard to which we have some metabolic data. Besides the great importance of calcium in the growth and repair of bone, for the teeth, and for the function of the nervous system we know it to be under the hormonal control of both the thyroid and parathyroid glands. Deposited in the bones, from which it is readily mobilized under a variety of influences, it is present in the blood in at least two forms —the ionized and the non-ionized—the calcium proteinate. Furthermore, pathology has long ago demonstrated the early and easy deposition of calcium in any area in which the tissues have become avascular, with fragmentation of the cells and intercellular substance. The administration of thyroxin has been shown to cause definite loss of calcium from the body, while the action of the parathyroids causes a reduction of the ratio of calcium to phosphorus in the blood. Furthermore, the continuous intake of a large amount of calcium, as under the régime of the Sippy diet, is frequently accompanied by renal stones which contain this substance.

As to the suggestions regarding the causation of stone, it has been thought in the past that the presence of obstruction within some part of the efferent urinary passages causing stasis might predispose to the precipitation of salts which otherwise would be held in solution. But very many cases of calculi, especially when small and early in their growth, are found in which there is no evidence of antecedent mechanical obstruction to pelvic or ureteral peristalsis. Stasis is probably more often the result of the stone than its cause.

Another suggestion relates to the ratio between crystalloids and colloids of the urine; the colloids by adsorption being assumed to hold the crystalloids in a supersaturated balance which is easily upset by an excess amount of the latter or a lessened amount of the former. It may well be that the crystalloids so held will be de-

posited on the surface of a stone once it has started to form, but this theory tells us nothing as to just what it is that sets the process in action.

In the third case there are those who hold that bacterial infection is the antecedent cause of stone, but this ignores the many instances seen in the clinic in which no cultural evidence of organisms is to be had. We know that there are many instances of renal stone which are sterile. This is not to say, however, that infection bears no relation to stone, for we are very familiar with instances in which the urine, being alkaline due to some urea-splitting bacterium, phosphatic stones recur with great speed and frequency. It is not clear, however, in such cases that the infection preceded the appearance of the first stone, for only too often both have been present long before the patient appears for examination.

A fourth condition as a result of which stones are found to form is related to endocrine dysfunction of the parathyroid glands. Here we are on firmer ground. Overaction of the parathyroids has been shown to cause a marked disturbance of the calcium-phosphorus ratio in the blood stream—a breakdown of the homeostasis—and to be accompanied by lesions in the bones in localized areas in which there is marked loss of calcium (osteitis fibrosa cystica). Along with this mobilization of calcium and consequent increase in its amount in the urine, there are changes in its phosphorus content as well. Clinical studies have shown the presence of calculi in well over 50 per cent of instances of hyperparathyroidism. On investigating cases of urolithiasis serially, however, it is found that a diagnosis of parathyroid dysfunction can be made in only about 5 to 7 per cent of the cases. We conclude, therefore, that though the disturbance in the calcium phosphorus ratio in the blood stream caused by hyperparathyroidism results frequently in the appearance of calculi in the kidney, it is a cause which is rather rare in the total incidence of stone.

The last and most important state, which since the observations of Mendel and others has been known to be accompanied by nephrolithiasis is that caused by a deficient bodily intake of vitamins, especially A, and to a less extent D.

Vitamin A deficiency causes an atrophy of epithelium and its replacement by keratinized cells. Its absence causes a starvation which is specific for many epitheliums. To quote Wolbach:

"The consequence (of this starvation) is atrophy, which progresses to a state wherein the cells, although having the appearances of viability, become inert in physiologic activities and in their role of covering membranes. An invariable sequence in pathology is that a break in the continuity of a tissue is followed by reparative proliferation. In vitamin A deficiency the basal cells normally concerned in maintaining the integrity of epithelium respond by active mitotic division. As the basal cells have a focal distribution in all non-stratified epitheliums, the next effect of the deficiency after atrophy is the appearance of scattered areas of proliferative activity beneath the original epithelium. The new (reparative) cells by their continued growth undermine and replace the original epithelium and, regardless of previous function and morphology of the region, develop into a stratified keratinizing epithelium."

Such cellular formation is directly comparable to keratotic areas of the skin of the old with which we are all familiar and which, in their superficial layers, at least, take on the aspect of an inert foreign material.

Along with these epithelial changes, which are most marked in the respiratory tract, the alimentary tract and the genito-urinary tract, there occurs in vitamin A deficiency a slowness in the regeneration of the visual purple of the retina. Thus is caused hemeralopia (night blindness)—and it is interesting that the test to dark adaptation has become one of the most delicate methods of determining a lack of this vitamin.

Twenty-four out of twenty-five patients having calculous disease were shown by Ezickson and Feldman to have a pathologic ocular response to the dark. Giving these patients a more liberal amount of this vitamin, however, failed to improve the ocular condition. In animals, however, all workers have been able to show not only a return of the changed epithelia to a normal configuration on resuming a normal diet, but also, as so thoroughly demonstrated by the observations of Higgins, there is caused, in many instances at least, a disappearance of the renal calculi. Following this lead Higgins has endeavored to relieve the condition of urolithiasis in human beings by the exhibition of a dietary high in vitamin A, with acid ash, accompanied by acidification of the urine to a pH as low as 4.5 or 5. Some diminution of the calculous formation has resulted, though this favorable effect is by no means constant or universal.

Turning now to local conditions in the kidney itself there has recently been brought forward some very important work by Randall which throws much light on the immediate pathogenesis of stone. From a large amount of autopsy material carefully examined, he has been able to demonstrate lesions at the apex of the renal papilla consisting of a calcium plaque underneath the epithelium on which, following erosion, stone-forming crystals will be or have been deposited. Without question such lesions represent the long assumed nidus which is the necessary starting point for the subsequent deposition of crystals eventually forming the calculus. Such conditions are shown also to take place without stasis of urine, and also on microscopic examination to be without evidence of inflammation.

Observations such as these are of the greatest importance for they lead us properly to undertake a much more thorough microscopic investigation of each renal papilla than has ever been the custom of the pathologist in the past. As Randall puts it, "the pathology of the renal papilla has yet to be written."

At first thought this actual demonstration of a focal lesion which acts definitely as the nidus for subsequent deposition of substances in crystalline form leads us to assume that this area is actually a localization of a vitamin A deficiency. But the histology does not bear out this assumption, for it does not show the keratinizing process characteristic of the vitamin A deficiency as we know it. On the contrary the description of Randall's material is as follows:

"The Calcium Plaque: Approximately midway between the tip and the base of the papilla, underneath the epithelial covering, is an area, measuring 2.5 mm. in length and varying from 0.1 to 0.3 mm. in width, composed of dense connective tissue. The surface of the papilla over this area is somewhat irregular. The blood vessels in this location are less numerous, and those present are partially obliterated by the surrounding dense connective tissue. Some of the collecting tubules are devoid of lining epithelium, while other tubules show cells evidencing degenerative changes. In the portion of this region nearest the tip there are a number of small areas showing granular detritus. In this location are seen two small irregular deposits of purplish-staining material measuring approximately 0.3 by 0.03 mm. By special staining methods these deposits proved to be calcium. These calcium deposits, or plaques, are separated from the surface of the papilla by a thin irregular layer of connective tissue and covering epithelium. Where the calcium

is less dense it occurs in rings, definitely deposited in the basement membrane and spreading into the ground substance of the surrounding connective tissue.

"Through the papilla, but especially near the tip, there are areas showing an increase of interstitial connective tissue. Some of the blood vessels show narrowing and irregularity of their lumina. The cortex and medulla show no noteworthy lesions. The walls of the convoluted tubules show no calcium deposits. The larger vessels show a moderate degree of arteriosclerosis. There is no microscopic evidence of infection in this specimem."

"Calculus on Plaque: Near the tip of the papilla, 0.3 mm. beneath the surface, there are irregular calcium deposits over an area 2.2 by 0.6 mm. Near these deposits, on the surface of the papilla, there is an irregular calcium plaque measuring approximately 0.4 by 0.1 mm. To the outer surface of this calcium plaque, and only to the plaque, is attached an irregularly shaped calculus measuring 1.75 by 0.8 mm. This stone, by special staining methods, was proven to be composed of calcium phosphate, while the plaque on which it grows stains for calcium but not for calcium phosphate."

This is not the occasion to indulge in speculation. It will be evident, however, that for the further study of the diverse problem of urolithiasis we have now a definite starting point. The question will now be: What conditions can be found which will cause a nutritional alteration of the cells in the renal papilla leading to subsequent deposition of substances brought to the urine by the blood? We are beginning to learn something about the vitamins, something about the action and interaction of the endocrine glands; we still need much further light on the normal and abnormal calcium metabolism, however. When it comes to the significance of a substance such as citric acid or the citrates in the bodily hemostasis or the action of such enzymes as phosphatase, we are still ignorant But in the pathologic changes of the renal papilla we can visualize much of great promise for future discoveries.

REMARKS BY THE PRESIDENT

PRESIDENT RANDALL: Gentlemen, in closing the meeting I have many thanks to extend. First of all, I want to thank each of you for your splendid response to the program, not only in the amount of material but the high scientific character that the meeting has brought forth.

I owe a very special thanks to Dr. Higgins. I am delighted that the Nominating Committee has made him full secretary and I feel confident that our Association is going to be safe in his hands.

I wish to thank you again for the orderly way in which the meeting has proceeded. It has been a great pleasure to preside over a meeting where men stuck to their time limits and quickly summarized their picture and where the discussion has been so good.

Of course, I owe you my personal thanks for allowing me to be in the chair, and I cannot elaborate on how great an honor I feel that this represents; it is a bit too deep.

To the younger members I wish to extend a welcome. We are delighted to have you here, and at the same time I feel like expressing a bit of jealousy that it is to be yours to go on so much longer, and the enjoyment that is ahead of you is always worthy of your attendance. In your hands we entrust the coming years of the Association, and I am sure that each of you will hold the torch high.

Now, I wish to call on the two Senior Ex-Presidents that are with us, Dr. Hagner, president in 1915, and Dr. Cunningham, president in 1921, to escort your new president, Dr. George Gilbert Smith, to the rostrum. (Applause.)

PRESIDENT-ELECT SMITH: All that I can say today is that I thank you very, very much indeed for this signal honor. As Sandy has so well said, it means more than anyone can say. I shall do my best to try to carry on according to the traditions of this Society, and I feel that with Dr. Higgins at my right hand, being my right hand, we will make it go somehow.

Thank you, very much! (Applause.)

DR. HAGNER: Mr. President, I want to move that we give a rising vote of thanks to our retiring president and to our new secretary for this very successful meeting.

The audience arose and applauded.

The meeting adjourned at one o'clock.